The Journal of
Obstetrics and Gynaecology of the British Empire

VOL. LXV, No. 5 NEW SERIES OCTOBER 1958

PREGNANCY TOXAEMIA ASSOCIATED WITH HYDROPS FOETALIS, HYDATIDIFORM MOLE AND HYDRAMNIOS*

BY

JAMES S. SCOTT, M.B., Ch.B., M.R.C.O.G.

From the Department of Obstetrics and Gynaecology
The University of Liverpool

A. MATERNAL REACTIONS TO RHESUS FACTOR ISO-IMMUNIZATION

FOLLOWING the discovery of the Rhesus factor it was for long believed that pregnancy associated with a state of iso-immunization carried no special hazards for the mother except in the event of an incompatible blood transfusion. Later it was recognized that, when the foetus dies *in utero* as a result of haemolytic disease, the mother can sometimes develop fibrinogen depletion or other haematological change which leads to blood coagulation failure. This condition, however, is not peculiar to Rhesus iso-immunization and can arise whenever a dead foetus is retained long *in utero*—irrespective of the cause of death.

The literature does, however, contain reference to cases in which there has been quite serious maternal illness associated with the carrying of a foetus severely affected by haemolytic disease. From a study of these cases it would appear that the maternal reactions fall into two groups: (i) those which suggest a haemolytic process, and (ii) those presenting a picture similar to, or identical with, that of pre-eclampsia.†

(i) This type of reaction varies. In an acute form it may be manifested by rigors and vomiting followed by evidence of haemolysis having occurred. The onset may, however, be insidious, and is then characterized by jaundice appearing in association with malaise and raised levels of bilirubin and bile acids in the blood. Early reports on this condition were by Rolleston (1910, 1920) who, writing on "grave familial jaundice of the new born", noted maternal jaundice in 15 out of 130 pregnancies. His description of the cases leaves little doubt that he was dealing with babies severely affected by haemolytic disease. Kaiser (1952) described 2 cases of maternal illness associated with hydrops foetalis, a feature of the illness being generalized pruritus associated with a high level of bile acids in the blood. Velez Orozco, Guerrero and Marvan (1950) claimed, in this connexion, that the severity of foetal haemolytic disease can be assessed by estimation of the level of haemolytic products in the maternal serum. Chown (1954, 1957) recounted cases in which he suspected that a maternal disturbance resulted from foetal haemorrhage into the maternal blood stream and Javert and Reiss (1952) described histological changes in the placenta which they attributed to such haemorrhages.

It would seem, therefore, that whereas certain of these maternal reactions, especially those with an acute onset, may be caused by incompatible foetal cells crossing the placenta and resulting in lysis in the maternal blood, others are the result of the products of haemolysis within the

* William Blair-Bell Memorial Lecture delivered at the Royal College of Obstetricians and Gynaecologists on 30th May, 1958.

† In view of a doubt as to whether pre-eclampsia is a specific disease or a syndrome which may be produced by more than one disease, the loose term "toxaemia" is generally preferred in this communication.

foetus entering the maternal circulation. There is nothing in the case records, however, to suggest that these illnesses are in any way related to the "toxaemia" which the mother sometimes develops and with which this communication is mainly concerned.

(ii) The maternal toxaemia described in association with severe foetal haemolytic disease is characterized by oedema, hypertension and albuminuria; some writers regarding it as true pre-eclampsia, others as something different. As with toxaemia in other circumstances, not all the three signs are necessarily present in one case. Rolleston (1920), Kaiser (1952), O'Driscoll and Lavalle (1955) and Goodlin (1957) all reported cases of toxaemia associated with severe haemolytic disease of the foetus, while McGaughey (1952) commented that the association is "well known". Potter (1947) described a maternal syndrome, occurring about the time of intra-uterine death of severely affected babies, which was characterized by albuminuria and oedema; this she regarded as being different from pre-eclampsia because the systolic blood pressure did not rise above 140 mm. Hg. Walker, Murray and Russell (1957) observed that the incidence of pre-eclampsia was doubled in mothers of stillbirths due to haemolytic disease and increased four fold when the foetus was hydropic. However, Dieckmann (1952), quoting Hurst, Taylor and Wiener (1946) and also Potter's review of 190 cases of haemolytic disease of all types, stated that the incidence of toxaemia is not increased in cases of Rhesus sensitization. Greenhill (1955) also declared that there is not an overall increase in the likelihood of toxaemia of pregnancy when a state of Rhesus iso-immunization arises. He went on to say, however, that when it does occur, the foetus is usually hydropic. Here would appear to be the crux of the matter. *Is toxaemia likely to occur in any case of foetal haemolytic disease or only when the foetus is dropsical?*

In an attempt to answer this question the records of the Liverpool Maternity Hospital and Mill Road Maternity Hospital for 4 years, 1953–1956, were examined.

The criteria used for the diagnosis of toxaemia in this and other studies reported here were the same as those used by Gemmell, Logan and Benjamin (1954) in their survey of all the 15,364 births in Liverpool during 1951. Toxaemia was diagnosed on the presence of any two of the following:

(i) A blood pressure of 140/90 or more.

(ii) Oedema.

(iii) Albuminuria without local cause.

Eclampsia was included as the most severe form. In regard to the interpretation of blood pressure readings, isolated rises during labour were ignored; blood pressures, in which either the systolic was more than 140 or the diastolic was more than 90 mm. of mercury, were included but not those where only systolic or diastolic equalled the critical figure when the other reading was normal (Gemmell, 1957). No attempt was made to distinguish between pre-eclampsia and essential hypertension in their study and the same is true of this one: both are included in the term toxaemia.

During this time 172 babies affected by haemolytic disease but *not* showing hydrops, were born. All the mothers were multiparous and only 8 of the pregnancies were complicated by toxaemia. This gives an incidence of 4·6 per cent which is not significantly higher than the 4·2 per cent expected incidence in the unselected Liverpool multiparous patients (Gemmell *et al.*, 1954). These findings lend support to the statements quoted above which go to show that Rhesus incompatibility in itself does not cause toxaemia of late pregnancy. It remains to be decided, however, whether hydrops foetalis is a predisposing factor.

B. Toxaemic Reactions to Hydrops Foetalis

(1) Literature

The many references in the European continental literature to an association between hydrops foetalis and toxaemia of pregnancy are reviewed by Jann (1954). He goes on to comment that, prior to the elucidation of the relationship of hydrops foetalis to other forms of haemolytic disease, and to the discovery of the Rhesus factor, the common occurrence of toxaemia in cases of hydrops foetalis was often recorded and was generally recognized. Recent knowledge, however, has obscured the situation and the

grouping together of all cases of Rhesus incompatibility has led to the neglect of older clinical observations. In this respect it is of interest to note that Burger (1947), being deprived by war conditions of knowledge of the Rhesus factor, was enabled to develop the theoretical implications of the maternal effects of hydrops foetalis beyond the stage reached by other writers before or since.

That hydrops foetalis had some connexion with maternal oedema and albuminuria was also well known in this country in the past. Ballantyne in 1902 gave a complete account of it and his, as well as other contemporary writings, were probably responsible for the statement that hydrops foetalis may be complicated by toxaemia of late pregnancy which has appeared in some British textbooks on obstetrics throughout this century.

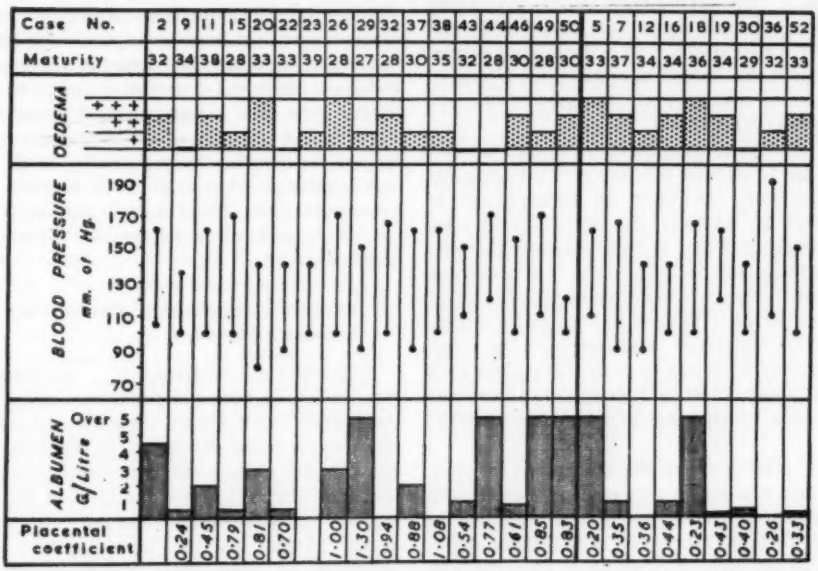
Of the many authors who have written on the subject, however, few have attempted to state statistically the incidence of toxaemia in cases of hydrops foetalis. The exceptions are Kloosterman (1947) and Kloosterman and Huidekoper (1954) who found toxaemia in 23 out of 35 mothers (65 per cent) who gave birth to a hydropic infant, and Jann (1954) who reckoned the incidence as being more than 70 per cent in the cases recorded in the literature. In these papers, however, and in those of other authors who describe individual cases there is much confusion over terms such as "toxaemia" and "pre-eclampsia". The standards used are not stated nor is any attempt made to compare the findings with controls. It was, therefore, decided to re-investigate the matter on a statistical basis.

(2) Material

The patients reviewed were those delivered of a hydropic foetus in the Liverpool Maternity Hospital, Mill Road Maternity Hospital and the

TABLE I

Twenty-six cases with toxaemia (50 per cent of total of 52 cases of hydrops foetalis)



The average placental coefficient in these cases was 0·62 whereas in the non-toxaemic cases the average placental coefficient was 0·38. The 9 cases (Number 5–52) to the right hand side of the heavy vertical line were cases of hydrops *not* due to erythroblastosis.

Birmingham Maternity Hospital during 8 years, 1950 to 1957. There were 52 such cases and the diagnosis of hydrops was beyond doubt in all. Forty-six babies were stillborn; the remaining 6 lived for no longer than a few hours. All but 3 of the mothers had had previous pregnancies.

(3) Findings

(a) *Jaundice*

One of the mothers of a hydropic foetus developed jaundice without any other significant signs. Jaundice in a second patient was accompanied by signs of toxaemia and by accidental antepartum haemorrhage followed by severe oliguria. Neither of these two cases was fully investigated so the cause of the jaundice remains uncertain.

(b) *Toxaemia*

Twenty-six out of the 52 women in the series (50 per cent) developed signs which fulfilled the previously stated criteria for the diagnosis of toxaemia. This high figure tallies reasonably with the collected figures of Jann (1954) and those of Kloosterman (1947) mentioned earlier. Addition of the 3 series together gives a total of 166 cases of toxaemia in 249 cases of hydrops foetalis (66 per cent).

For statistical purposes, it would be unwarranted to assume that the over-all toxaemia incidence was the same in Birmingham as Liverpool. If, however, the 32 Liverpool cases are considered alone (30 multiparous) the incidence of toxaemia is found to be 15 whereas the expected incidence according to the figures of Gemmell *et al.* (1954) is 1·5 cases—a highly significant difference statistically. The high incidence of toxaemia is even more significant than the figures show for it frequently occurred in pregnancies which terminated as early as 28–32 weeks.

In the present series, the appearance of signs of the maternal illness very often coincided with the making of a firm or tentative diagnosis of hydrops foetalis. Moreover, they became manifest relatively early in pregnancy. The toxaemia was generally of severe degree (Table I); one woman died from the disease and another 8 were critically ill—2 having to be delivered abdominally on account of the toxaemia.

The details of the fatal case were as follows:

Case 23. Mrs. F. D., aged 43, was an 8-gravida whose blood group was O Rh negative with antibodies present. Her first 4 pregnancies were uneventful and resulted in the delivery of healthy babies. The fifth baby was macerated at birth and the sixth, although born alive, died in the neonatal period from haemolytic disease; the seventh was healthy. During this woman's last and fatal pregnancy, at the 37th week she developed oedema and slight hypertension (150/90, 140/100 mm. Hg). There had been no evidence of toxaemia in any of her previous pregnancies. Labour at term had to be assisted in the second stage with forceps because of the large foetal trunk. An 8 pounds 12 ounces fresh stillborn hydropic infant was delivered, followed by a large, pale, oedematous-looking placenta and a blood loss of 15 ounces. The operation was carried out under local anaesthesia and immediately after delivery the patient complained of pain in the epigastrium and chest; a state of shock developed and she died 3 hours later despite resuscitative measures. Examination of a blood sample revealed afibrinogenaemia but excessive haemorrhage was not a feature.

The signs of pre-eclampsia having been of the mildest, the maternal death was regarded as possibly due to amniotic or fibrin embolism. Post-mortem examination, however, showed macroscopic liver haemorrhages similar to those seen in eclampsia. Histologically these proved to have a periportal distribution and to be of the "lake" type. The kidneys showed intracapillary fibrils in the majority of the glomeruli; congestion of the capillary loops; glomerular thrombi; and hyaline droplets in the cells of some of the proximal tubules. These changes were considered to be typical of hypertensive toxaemia of eclamptic type.

(c) *Accidental Antepartum Haemorrhage (Abruptio Placentae)*

Accidental antepartum haemorrhages occurred in 13 cases (25 per cent). In 5 of these there were also signs of toxaemia and they are included in group (b) above. In one patient the placenta was praevia but concealed haemorrhage had also occurred above the level of the lower segment attachment. Although its severity varied (Table II), the bleeding was always sufficient to have real clinical significance; trivial shows (so-called minor accidental haemorrhages) were not included.

TABLE II

Hydrops Foetalis Cases with Accidental Ante-Partum Haemorrhage

	Maturity in weeks	"Toxaemia"	Blood loss		Remarks
			Revealed	Concealed	
Case 3	35	No	20 ounces	—	25 ounces P.P.H.
Case 6	40	No	Slight	8 ounces	
Case 9	32 (delivered 34)	Yes	2 ounces	Slight	Not haemolytic disease
Case 15	26 (delivered 28)	Yes	20 ounces+	20 ounces	30 ounces P.P.H. Repeated losses
Case 17	28	No	20 ounces	—	
Case 24	38	No	Slight	Moderate	
Case 31	28 (delivered 29)	No	40-60 ounces	10 ounces	Repeated losses. Placenta low lying
Case 32	28	Yes	—	10 ounces	Jaundice, oliguria for 6 days
Case 37	30	Yes	20 ounces	10 ounces	
Case 43	32	Yes	10 ounces	12 ounces	
Case 45	30	No	6 ounces	8 ounces	
Case 47	28	No	30 ounces	10 ounces	
Case 48	35	No	Moderate	—	

Total: 13 cases (25 per cent of the 52 cases of hydrops). Five of the cases had toxaemia.

Counting only once cases with both accidental haemorrhage and toxaemia, the combined incidence of the two conditions was 34 (65 per cent).

The frequent occurrence of antepartum haemorrhage is of considerable interest. A figure for the expected incidence of this condition is not readily available for comparison but, in the annual statistics of the hospitals in question, the percentage of the total deliveries complicated by accidental haemorrhage ranges from 1·5 to 5 per cent. Many of these cases are emergency admissions to the hospitals, having been booked for delivery elsewhere, so it is probable that the overall incidence of this abnormality in the total obstetric population is less than this; textbooks put it at 0·5 per cent or less. However, even if the highest figure of 5·0 per cent be taken for comparison, the incidence of 25 per cent in association with hydrops foetalis is significantly raised (possibility of a chance finding = 0·000004).

Like the signs of toxaemia, antepartum haemorrhage in these cases tended to occur at an unusually early stage in pregnancy (Table II). Often the clinician noted at the time that the uterus was larger than expected for the period of gestation and that it had a "doughy" consistency on palpation. Indeed, in 2 patients a provisional diagnosis of hydatidiform mole was made and in one this was still considered a possibility after radiological demonstration of a foetal skeleton. In another 2 cases it was recorded at the time of delivery that the placenta had appearances which resembled those of a hydatidiform mole (Fig. 1). This observation is by no means unique; Ballantyne (1902) quotes Jakesch (1878) who described the delivery of the placenta in these cases as being comparable to "the slow rolling forth of wool from an overfilled torn woolsack", a graphic description which could apply equally to the passage of a hydatidiform mole (Fig. 2). Herrnberger (1940) studying case records in the literature also noted the difficulty in distinguishing between the two conditions.

As always with accidental antepartum haemorrhage, the problem occurs as to whether it is caused by toxaemia of pregnancy. In this connexion it will be noted (Table II) that signs of toxaemia were present in less than half the cases of haemorrhage yet the toxaemia incidence

in the whole series was 50 per cent. It is therefore tempting to look for another cause. It seems possible, if not probable, that the separation of the placenta is a mechanical response to the bulk of the hydropic placenta and that the mechanism of haemorrhage is similar to that in hydatidiform mole—a condition which, as will be seen later, has yet other similarities.

C. The Cause of Toxaemia in Cases of Hydrops Foetalis

Since there seems no doubt that pregnancy toxaemia of quite severe degree is commonly seen when the foetus is hydropic, the question arises as to the cause and effect relationship. Older writers, as discussed by Ballantyne (1902) for example, considered that the oedema of the foetus and placenta was secondary to, and caused by, the maternal illness. This view is no longer tenable, if only because the foetus is not affected in the common type of pre-eclampsia seen in primigravidae and in other states when the mother becomes grossly oedematous. Modern knowledge makes it necessary to regard the foetal condition as *causing* the maternal disturbance and it might so operate by one of three mechanisms:

(i) A relatively massive transfer of foetal blood (or its breakdown products) into the maternal circulation, or a side effect of the antigen—antibody disorder associated with Rhesus incompatibility, might in themselves cause the toxaemia in the mother. In this connexion, Jann (1954) went so far as to suggest that the maternal signs are caused by a pressor substance liberated by the foetal kidneys in response to haemolysis.

(ii) Excessive distension of the uterus, caused partly by the bulk of the foetus and the placenta and partly by hydramnios which sometimes complicates hydrops foetalis, could be responsible, according to one present-day theory of the aetiology of pre-eclampsia.

(iii) Abnormal activity of the placenta itself might cause a maternal upset—as in the case of hydatidiform mole.

These three mechanisms are discussed in turn.

(1) An Antigen-Antibody Reaction

Although there is a certain amount of inconclusive evidence that a sudden transfusion of foetal blood into the maternal circulation does sometimes occur, producing a serious and dramatic reaction, the signs, as emphasized earlier, are quite different from those of pre-eclampsia. The complication is, moreover, rare. It may be added that in 3 of our cases in which foetal hydrops was complicated by severe toxaemia, the maternal blood was examined for foetal haemoglobin with negative results.

The toxaemia-like response of so many mothers is very unlikely to be the result of iso-immunization because it is fairly clearly established that the signs are only found when the foetus is hydropic. Blood destruction is equally extensive in other severe forms of erythroblastosis but it does not cause toxaemia.

It is not always realized that some 25 per cent of cases of hydrops foetalis are not caused by haemolytic disease—although Ballantyne (1896, 1902) expressed the belief that the condition, like dropsy arising after birth, could have several causes. In one of Seeger's (1670) cases he attributed the disease to the mother drinking large quantities of beer! This sort of aetiology may not now be accepted but it remains necessary to recognize that hydrops foetalis not resulting from iso-immunization is by no means uncommon. There are 11 such cases among the 52 reported here and toxaemia complicated 9 of these pregnancies. In each case the foetal and maternal bloods were exhaustively examined to exclude all forms of iso-immunization. The number of cases is small but the findings, when taken in conjunction with other evidence, offer strong support for the view that the cause of toxaemia is not the haemolytic disease but something connected with the hydropic change in the foetus and placenta (Figs. 3 and 4).

(2) Over-distension of the Uterus by Hydramnios and Bulky Products of Conception

For this to be considered as the operative mechanism in the production of the toxaemia three questions require to be answered: (*a*) Does hydrops foetalis cause hydramnios? (*b*) Does

hydramnios *per se* predispose to toxaemia? (*c*) Does over-distension of the uterus predispose to toxaemia?

(*a*) The increased incidence of hydramnios in association with hydrops foetalis is recorded by Ballantyne (1902) and by Henderson (1942) but the latter and Macafee (1950) both point out that the grossly oedematous foetus with its large placenta may lead to a mistaken diagnosis of hydramnios. Personal experience confirms that this is a real problem and that it can be extremely difficult to say on clinical examination whether hydramnios is present or not. Nevertheless, in 3 cases of this series measured quantities of more than 3 pints of liquor were removed at amniotomy while in 4 others a clinical impression of hydramnios was supported by a torrential gush of liquor when the membranes ruptured. The mechanism causing the hydramnios is almost certainly the inability of the foetus to swallow owing to the gross oedema of its cheeks, lips and fauces (Fig. 5); unless circumoral oedema is gross the amount of liquor is usually normal (Scott and Wilson, 1957). It can be concluded that hydrops foetalis can under certain circumstances cause hydramnios and that, even in those cases where it does not, the increased bulk of the foetus and placenta is likely to lead to excessive uterine distension.

(*b*) It is commonly assumed that hydramnios *per se* can cause, or favour the development of, pre-eclampsia. Theobald (1955), however, is critical of this view and emphasizes the remarkable lack of statistically acceptable evidence. He points out that hydramnios is often secondary to factors which in themselves may determine the occurrence of toxaemia by some mechanism other than uterine over-distension.

Macafee (1950) in a review of 147 cases of hydramnios reports a 24 per cent incidence of toxaemia but in his original paper he does not mention which of the cases occurred in association with other factors which, in themselves, are known to predispose to pre-eclampsia. This point, however, he elaborated later in a personal communication quoted by Theobald (1955).

At Mill Road Maternity Hospital, Liverpool, during the 8 years 1948-1955, there were 169 cases of hydramnios, 144 amongst women booked for hospital delivery for other reasons and therefore under continual observation. The criteria used for diagnosing hydramnios were those reported previously (Scott and Wilson, 1957): (i) the recording of clinical evidence of an excessive amount of liquor by two independent observers on at least two separate occasions during late pregnancy, or (ii) the recovery of more than 1,500 ml. of liquor at amniotomy.

The total number of cases of toxaemia in this series was 27 (16 per cent) in comparison with Macafee's 24 per cent but our diagnostic criteria may have been different from his. There were another 30 patients in our series who developed gross oedema, mainly of the lower limbs, but showed no other sign of toxaemia; these were excluded.

The cases of hydramnios were further analyzed by dividing them into two groups: (i) those in which there was an associated factor which could have predisposed to toxaemia by some mechanism other than simple uterine over-distension, and (ii) those in which the hydramnios was not obviously associated with any condition which in itself might have caused toxaemia.

Group (i)

In this category were 13 cases of twin pregnancy, 4 of hydrops foetalis and 4 pregnancies in diabetic women. This makes a total of 21 pregnancies of which 11 (52 per cent) were complicated by toxaemia.

Group (ii)

The remaining 148 cases are placed in this group although the cause of hydramnios was not discovered in 98. The underlying cause in the other 50 cases (details of which are given elsewhere, Scott and Wilson, 1957) was a gross foetal malformation. Only 16 of the 148 pregnancies (11 per cent) were complicated by toxaemia. Forty-three of the patients in this group were primigravid and 105 were multigravid. The expected incidence of toxaemia in this hospital's obstetric population is 10·7 per cent in primigravidae and 7·9 per cent in multigravidae (see statistics for Hospital "D" in the report by Gemmell *et al.*, 1954). It can be

calculated from these figures that the number of cases of toxaemia among this group of 148 patients would be expected to be 13. The difference between the expected and actual number of cases of toxaemia is not statistically significant.

From this analysis it may be concluded that, whereas review of all cases of hydramnios does show an increased incidence of toxaemia, this is only because of the inclusion of cases of multiple pregnancy, maternal diabetes and hydrops foetalis. There is no evidence that hydramnios unassociated with these states predisposes to toxaemia.

(*c*) If hydramnios *per se* is not associated with a significantly raised toxaemia incidence the main evidence for supposing that uterine over-distension can cause pre-eclampsia becomes invalid. The only other causes of over-distension which are quoted in support of this theory are multiple pregnancy, hydatidiform mole and hydrops foetalis; in all of these there is an alteration in placental function which, as will be shown later, is a more likely aetiological factor in the toxaemia associated with these conditions.

(3) Abnormal Placental Activity

The placental change in hydrops foetalis is sometimes regarded as merely one of passive oedema, such as occurs in the foetal tissues, with possibly some abnormal haemopoietic activity added. However, as Hellman and Hertig pointed out in 1938, the villi, in addition to being blown out with oedema, show clear histological evidence of over activity of the trophoblast with a well-developed Langhans' layer which is most unusual for late pregnancy. These Langhans' cells have been described as "persistent" but it seems quite possible that their presence represents a regeneration of tissue which disappeared in the normal way in mid-pregnancy only to reappear later in response to severe haemolysis or some other factor (Figs. 6, 7, 8, 9 and 10).

The degree of syncytial degeneration is also usually less than in a normal placenta of comparable maturity while both trophoblastic layers show increased vacuolization. Although there is evidence that the vascularity of the villi is deficient, the stroma of the villi is, as was pointed out by Kloosterman (1947) and others, distinctly hyperplastic. Indeed, the over-all appearance of the placenta of the hydropic foetus suggests unusual activity and an absence of the degenerative changes usually associated with advancing maturity.

The view that it is the placenta itself which is responsible for the development of signs of toxaemia is further supported by a study of the weight of the placenta in relation to the weight of the foetus—the so-called "placental co-efficient". In the normal case this co-efficient is approximately $1/5 = 0{\cdot}2$. In the series of cases of hydrops foetalis forming the basis of this communication the average placental co-efficient in those patients who showed signs of toxaemia was $0{\cdot}64$ whereas it was only $0{\cdot}37$ in those who remained well. This finding agrees with the observations of Kloosterman (1947) whose comparable figures were $0{\cdot}75$ and $0{\cdot}47$. The fact that the likelihood of toxaemia is dependent on the presence of a placenta which is heavy in relation to foetal weight emphasizes that the placental change is one of active hyperplasia and not merely one of passive oedema proportional to the foetal dropsy. This is further borne out by evidence of increased functional activity of the chorion in these cases, as measured by chorionic gonadotrophin excretion. This was not realized in the early part of this investigation and it has been tested in only the last 2 cases in which women carrying hydropic foetuses developed toxaemia at the thirtieth week of pregnancy. The urine in both instances gave a positive Aschheim-Zondek reaction in a dilution of 1 in 100. Greater dilutions were not examined but the results as they stand indicate a remarkably high level of gonadotrophin excretion for the particular stage of pregnancy. At the time of their deliveries, the babies and placentae weighed:

(i) Placenta, 4 pounds 4 ounces: Baby, 5 pounds. Placental co-efficient $= 0{\cdot}85$ (Case 49).

(ii) Placenta, 3 pounds 4 ounces: Baby 3 pounds 15 ounces. Placental co-efficient $= 0{\cdot}83$ (Case 50).

Herrnberger (1940) and Zsigmond (1941) also recorded the finding of a high gonadotrophin production in similar cases.

In view of these observations it is not surprising that theca lutein cysts are occasionally

FIG. 1

Enlarged view of hydropic placenta, showing bulky villi in upper part of picture which might be mistaken for early hydatidiform change.

FIG. 2

Like "The slow rolling forth of wool from an over-filled torn woolsack", is a description that could equally apply to the hydatidiform mole shown above.

FIG. 3

Case 51. Hydropic foetus and placenta not due to haemolytic disease. (Baby 5 pounds 15 ounces. Placenta 1 pound 14 ounces. Placental coefficient 0·37.)

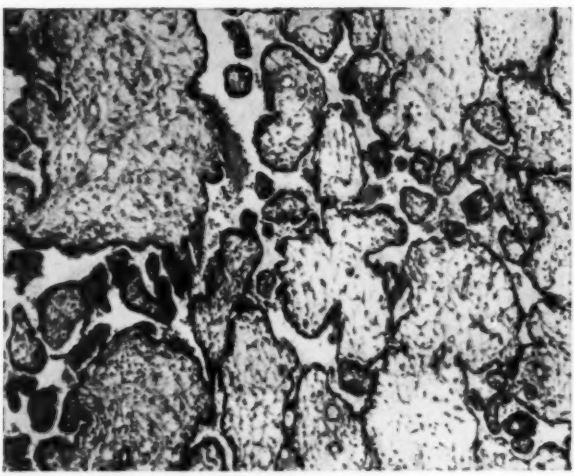


FIG. 4

Section from placenta of case of hydrops foetalis not due to haemolytic disease (Case 36). Note similarity to Figs. 7 and 9. ×70.

FIG. 5
Case 49 of the present series showing gross circumoral oedema. Considerable hydramnios was present.

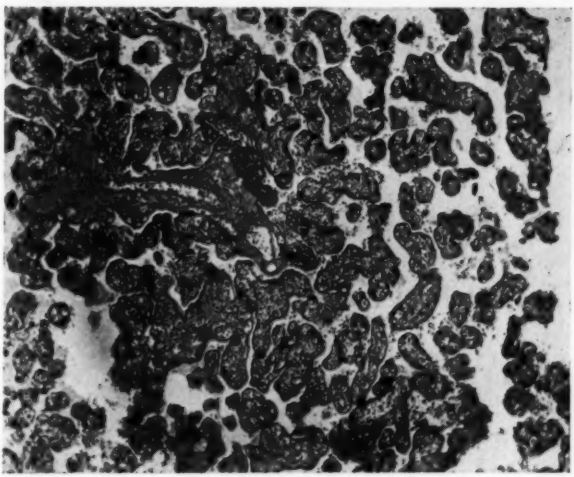


FIG. 6
Normal placenta of third trimester. Magnification the same as Figs. 4, 7, 9, 10 and 11. ×70.

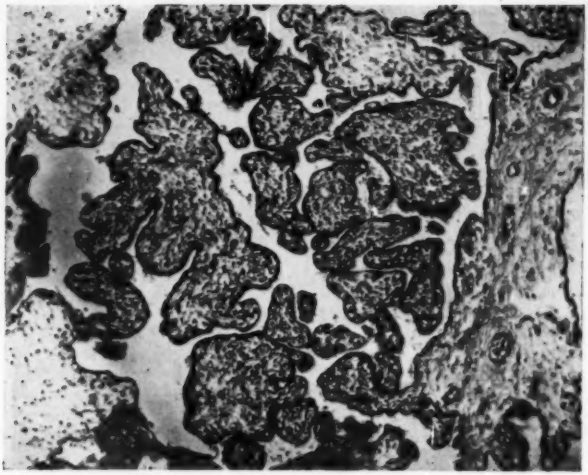


FIG. 7

Section from placenta of hydrops foetalis due to haemolytic disease (Case 49), in which the cellular hyperactivity is the oustanding feature. Note the cellular stroma and the presence of Langhans' layer of the trophoblast, which is clearly seen in the high power view (Fig. 8). ×70.

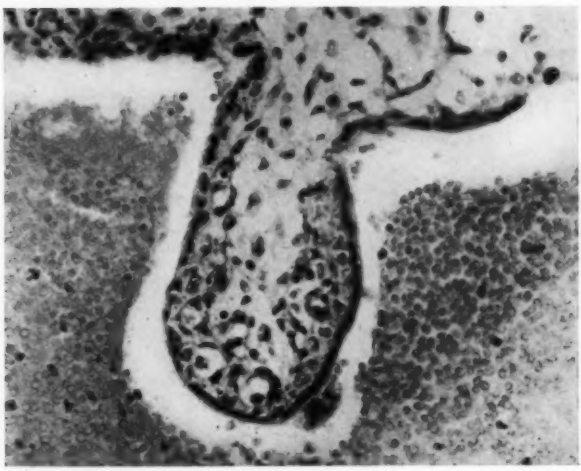


FIG. 8

High power view of placenta from haemolytic disease hydrops (see Fig. 7) showing presence of Langhans' layer (Case 49). ×290.

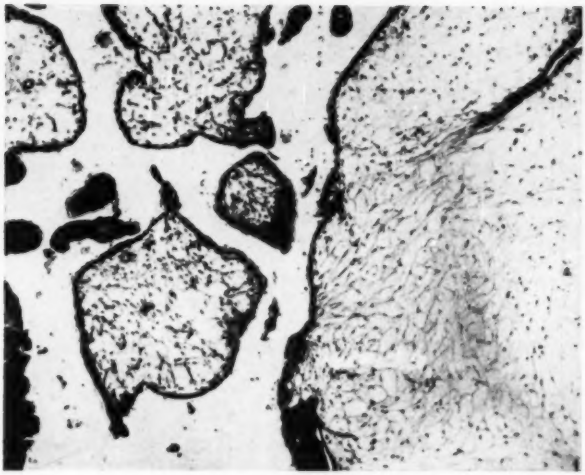


FIG. 9

Placenta from case of hydrops foetalis due to haemolytic disease (Case 50), showing a distinct similarity to hydatidiform mole (Fig. 10). ×70.

FIG. 10

Section of hydatidiform mole; note similarity to Fig. 9, illustrating erythroblastotic hydrops placenta of dropsical type. ×70.

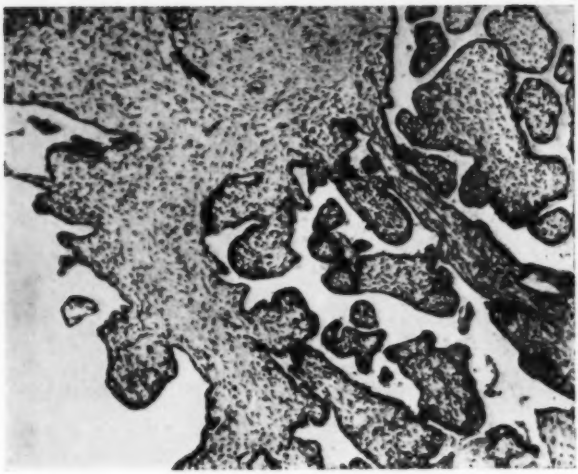


FIG. 11

Section from placenta of Mrs. E.L. Case of "hyperplacentosis". Note cellularity of villi and immaturity of trophoblast for 37 weeks. See Figs. 7 and 12. ×70.

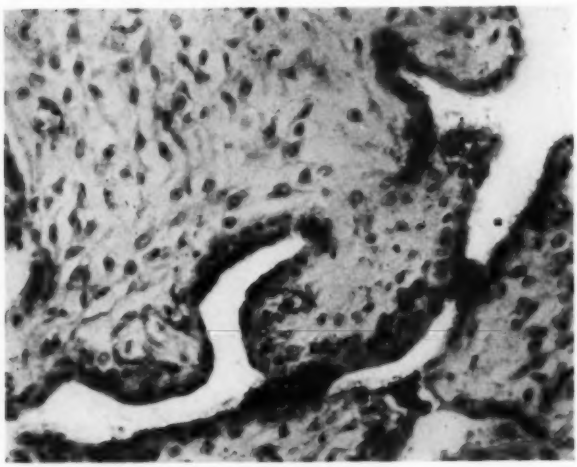


FIG. 12

High power view from placenta of Mrs. E.L. Case of "hyperplacentosis", showing presence of Langhans' layer at 37 weeks. (See Fig. 11.) ×290.

found in the maternal ovaries in association with hydrops foetalis. Burger (1947) reviewed 4 such cases. In one of Jann's (1954) series of hydrops foetalis, laparotomy was performed for a pelvic tumour discovered on examination during the puerperium; the tumour proved to be bilateral ovarian theca lutein cysts. Cases have also been reported by Schultheiss-Linder (1942) and Lermer, Villanueva and Tannhauser (1958).

As the evidence collects it becomes increasingly apparent that the clinical similarity between hydrops foetalis and hydatidiform mole noted earlier, is accompanied by a pathological and functional similarity. This similarity extends even to the histological features of the chorion in the two conditions for, as Hellman and Hertig (1938) pointed out, both are characterized by: (1) hydropic swollen villi with relatively avascular cores, (ii) excessive trophoblastic activity and (iii) vacuolization of the epithelial cells (Figs. 9 and 10). In hydrops placentae, as in hydatidiform mole, the picture varies between one in which the increased cellular activity is the prominent feature and one in which the villous oedema predominates (Figs. 7 and 9).

Thoughts directed along these lines raise several questions. For example: (i) is there more chance of chorionepithelioma after the birth of a hydropic foetus than after a normal foetus? (ii) Does a study of hydrops foetalis offer a clue to the aetiology of hydatidiform mole? (iii) Is the placental change sometimes more important in causing intra-uterine death of the hydropic foetus than haemolysis? The answers to these and allied questions are unknown, and it suffices to conclude this argument by adding that both hydatidiform mole and hydrops foetalis frequently cause a pre-eclampsia-like syndrome with special features which are discussed later. Here it may be noted that, although an association between toxaemia and hydatidiform mole has long been assumed and described, its existence was not established statistically until the work of Page in 1939. He found that mole formation increased the incidence of toxaemia 8 times in pregnancies carried beyond the third month—a figure very similar to that obtaining in the cases of hydrops foetalis reviewed here.

In line with the above observations, it is relevant to point out that Ten Berge and Van Assen (1947) noted a relationship between placental hyperplasia and toxaemia in the diabetic patient. The placenta from diabetic women often has a histological appearance of "immaturity" and on microscopic examination can be confused with the hydropic placenta. Finally, in this context, it may be recalled that the well-known work of Smith and Smith (1940) indicated that the gonadotrophin excretion of the pregnant diabetic woman is relatively high—an observation later confirmed by Loraine (1949a).

Whether the same arguments are valid for multiple pregnancy remains to be established but it is possible that here again the incidence of toxaemia may be related to the relative weights of the placentae, if not to the histological appearances of the trophoblast. That there is often excessive chorionic activity in these cases is suggested by the well-established observation that the excretion of chorionic gonadotrophin is sometimes so high as to make it difficult for the clinician to differentiate between hydatidiform mole and multiple pregnancy in the early months of gestation.

D. The Features of the Toxaemia Associated with Hydrops Foetalis and Hydatidiform Mole

The toxaemic syndrome which frequently complicates hydrops foetalis and hydatidiform mole has some special features which raise the questions as to whether it represents a particular form of pre-eclampsia and whether pre-eclampsia is a single disease entity.

In the first place the syndrome appears earlier in pregnancy than is usual for pre-eclampsia as seen in the otherwise normal gravida. Moreover, the manifestations of hypertension, albuminuria and oedema are often of severe degree. Despite this, however, the patients rarely have eclamptic fits. Jann (1954) collected 124 cases of pre-eclampsia associated with hydrops foetalis from the literature and in none had the patient had fits. The same is true of the 26 cases described here, even in the case of the patient who died and in whom histological changes "typical of eclampsia" were found in the liver and kidneys at autopsy.

Similar observations with regard to the infrequency of fits in cases of toxaemia associated with hydatidiform mole are made by Acosta-Sison (1956, 1957), and Theobald (1955). The latter says that eclamptic convulsions have never been seen as a complication of hydatidiform mole by any living English author, but Chesley, Cosgrove and Preece (1946) recorded a case in America and reviewed other alleged cases but not all of these had fits. Acosta-Sison records 2 fatal cases in which, despite the absence of fits in life, histological features of eclampsia were found at autopsy. His experiences tally closely with the personal one described above in relation to hydrops foetalis.

E. The Aetiology of the Pre-Eclamptic Syndrome

In discussing the underlying cause of the maternal toxaemia which occurs in association with hydrops foetalis and hydatidiform mole, care has so far been taken to avoid the matter of the aetiology of pre-eclampsia in general. The reason for this is a very real doubt as to whether the statistician's and clinician's arbitrary definition of "pre-eclampsia" covers more than one disease entity. However, the results of this investigation do have some bearing on views as to the aetiology of this obscure maternal reaction to pregnancy.

The evidence presented here does not in any way lend support to the utero-renal reflex theory, so persistently advocated by Sophian (1953), in which uterine over-distension is regarded as a major aetiological factor in pre-eclampsia. On the contrary, the analysis of the cases of hydramnios confirms Theobald's suspicion that the adherents to the uterine distension theory have been too ready to reach assumptions which are not supported by controlled observations. Next it may be stated that the findings and arguments presented here, which go to show that one particular pre-eclamptic syndrome is dependent on placental changes, are not incompatible with the placental ischaemia theory of toxaemia, associated particularly today with the names of Page (1953) and Bastiaanse and Mastboom (1949, 1950). Indeed, the finding of the chorion in a primitive state in these cases could be a response to cellular anoxia though such an idea raises many problems with which it is not possible to deal here.

Placental changes in structure, function or both appear to be a feature of many cases of pre-eclampsia but the changes are not always the same. Indeed, they appear to fall into two distinct and apparently contradictory classes. On the one hand there is the placenta in which the normal ageing process fails to take place and in which the trophoblast (and especially Langhans' layer) is hyperplastic. This type of change is a feature of pre-eclampsia as it occurs in association with hydrops foetalis, hydatidiform mole, maternal diabetes and possibly multiple pregnancy and is frequently, if not always, associated with an excessive production of gonadotrophin. On the other hand, the placenta in many other cases of toxaemia occurring apart from the conditions mentioned above, often shows evidence of infarction and acceleration of the normal ageing process with, presumably, a decrease in functional activity. Histologically the amount of active trophoblastic tissue is reduced in these cases and this appearance tends to be associated with a diminution in the production of progesterone (Russell *et al.*, 1957; Paine, 1957).

It could be rationally postulated that whatever may be the adrenal and pituitary hormone interreactions bringing about its manifestation, the maternal disturbance labelled "pre-eclampsia" results primarily from an imbalance between the two different trophoblastic elements of the placenta. In one group of cases the Langhans' layer, the gonadotrophin producing cells (Wislocki *et al.*, 1948) is over-active while in the second group the syncytium, the steroid hormone producing zone, is under-active. The latter mechanism may operate when the placenta shows evidence of premature senility or degeneration—changes which are for the present assumed to precede and cause the pre-eclampsia. They could however, be the result of hypertension and not its cause. This, in fact, is a conclusion reached independently by Burstein, Herman and Soule (1957) whose study of placentae from an unselected series of cases of toxaemias led them to postulate that all degenerative changes are, like the hepatic and renal lesions, secondary to

hypertension whereas chorionic over-activity evidenced by "syncytial budding" might have an aetiological role in the disease.

The idea that the toxaemic process is associated with an imbalance of the steroid and gonadotrophic hormones secondary to an underlying alteration in the trophoblastic components is similar to that which Smith and Smith (1937, 1940) postulated, but they arrived at it from an entirely different approach. Though the Smiths' findings have received a considerable measure of confirmation by different workers such as Loraine (1949b), Loraine and Mathew (1950) and Govan (1952) yet definite proof or disproof of their validity and relevance has been extremely elusive. There does not, however, appear to have been a systematic attempt to integrate the various hormonal changes with the trophoblastic anatomy.

F. Is "Pre-Eclampsia" an Entity?

At several points in this paper doubt has been expressed as to whether or not all patients labelled as suffering from "pre-eclampsia" do in fact have the same disease. In recent years there has been an increasing demand for the application of definite arbitrary standards to the diagnosis of the condition. These were introduced mainly for statistical purposes but have tended to hinder a rational approach to the elucidation of the problem. There is no other disease in medical practice the diagnosis of which is made automatically on the presence of 2 out of 3 physical signs. Bearing in mind the "occult oedema", the lability of the blood pressure and the changes in the peripheral capillary bed in pregnancy (Landesman, Douglas and Holze, 1954; Landesman, 1958), which are recognized physiological reactions to pregnancy, is it surprising that oedema, hypertension and albuminuria are common in pregnancy and are they reliable signs on which to diagnose a specific disease? Govan *et al.* (1951) have produced suggestive evidence that in toxaemic hypertension of pregnancy different types of hypertension occur, depending upon whether or not there is a related elevation of gonadotrophic production. Similar doubts exist in regard to eclampsia. The occurrence of convulsions, to which children, like pregnant women, are prone, has for long ceased to be an adequate diagnosis *per se* in the paediatric world, whereas a diagnosis of eclampsia satisfies most obstetricians.

It would seem worth bearing in mind that an excessive amount of an electrolyte such as potassium can produce signs and symptoms very similar to a deficiency of the same substance; in diabetes, hypoglycaemia and hyperglycaemia both produce coma but the mechanism is entirely different. The possibility of a comparable situation in relation to the pre-eclamptic syndrome must be considered before accepting a common background for all the cases. Even the evidence of the morbid anatomists is not necessarily conclusive; the renal and hepatic changes regarded as typical of eclampsia cases may be simply the result of a hypertensive process superimposed on the physiological pregnancy changes in the capillary bed.

It may well be, therefore, that the importance of the observations reported here lies not in any bearing they may have on a particular aetiological theory of pre-eclampsia but in their support for the concept that the clinical syndrome, at present automatically labelled "pre-eclampsia" by arbitrary standards, may be a manifestation of more than one disease, or it may be one disease with different sub-groups and with a variable underlying cause. On the evidence so far available it can be stated that from a hormonal, pathological and clinical standpoint the toxaemias associated with hydrops foetalis and hydatidiform mole come into one category which could be regarded as a state of "hyperplacentosis". Further investigation may confirm the suspicion that the toxaemia associated with diabetes mellitus and multiple pregnancy belongs to the same category. It is even possible that certain cases of pre-eclampsia which occur without any obvious gross abnormality in the mother or her conceptus are also a manifestation of "hyperplacentosis".

A case encountered recently supports this idea:

Mrs. E.L. gave a history of 3 pregnancies and 1 miscarriage, none of which had been complicated by toxaemia. She was admitted to hospital when 37-weeks pregnant with signs of severe pre-eclampsia. The highest blood pressure reading was 180/100; oedema was present and albuminuria rose to 20 grams per litre. The foetal

heart sounds disappeared shortly after admission but despite this the pre-eclamptic signs continued to increase in severity. Labour was induced by rupture of the membranes and oxytocin drip infusion. A non-hydropic macerated foetus weighing 5 pounds 8 ounces was delivered followed by a large placenta weighing 2 pounds 11 ounces. The placenta was in every respect identical to that found in hydrops foetalis (Figs. 11 and 12). The mother's blood group was A Rhesus positive and there was no serological evidence of any form of iso-immunization.

If the concept of "hyperplacentosis" is accepted as the underlying explanation of one form of pre-eclampsia it is not necessarily applicable to all. There are many cases in which pre-eclampsia is characterized by a small and under-active placenta but whether this is a cause or an effect remains to be established.

Theobald has said "there is not one eclampsia but several". The same is surely true of pre-eclampsia. Might not more progress be made in the understanding of the "disease of theories" if our present definition of "pre-eclampsia" were regarded as a "theory of diseases"?

Summary

Maternal illnesses occurring in pregnancies complicated by Rhesus iso-immunization are reviewed. These only afflict patients carrying hydropic foetuses and in most cases the illness appears indistinguishable from toxaemia of pregnancy. In 52 cases of hydrops foetalis of varied aetiology, the incidence of toxaemia was 50 per cent. The possible causes of the toxaemia in these cases are discussed. The mechanism is unlikely to be related to overdistension of the uterus as a review of a series of 148 cases of uncomplicated hydramnios showed no significant increase over the expected incidence of toxaemia. The abnormal placenta associated with hydrops foetalis, however, does appear to be directly related to the high toxaemia incidence. This placental change is not merely a passive oedema but is an active hyperplasia associated with qualitative alterations in the trophoblast, which shows a clearly distinguishable Langhans' layer even in the last trimester.

The similarity of the placental changes in these cases to those of hydatidiform mole is striking and this extends also to many clinical features, including some which suggest that there is a similar hormonal disturbance.

The observations recorded are discussed in relation to ideas concerning the aetiology of pregnancy toxaemia. Cases of toxaemia occurring in association with hydrops foetalis and hydatidiform mole form a group which may differ fundamentally from cases of pregnancy toxaemia occurring in other circumstances.

Acknowledgments

I am grateful to the consultant staff of the hospitals concerned for permission to review these cases. To Professor T. N. A. Jeffcoate I am greatly indebted for much help, encouragement and advice in the preparation of the paper. My thanks are also due to Sir Arthur Gemmell, Dr. J. B. Lynch and Dr. Olive Sharpe for reading the manuscript and for their helpful suggestions on different aspects; to Dr. A. S. Woodcock for the photomicrographs; to Professor H. L. Sheehan for the histological sections of Case 23; to Dr. D. C. A. Bevis and Professor Bruce Chown for references; to Mr. R. L. Placket for help with the statistical aspects; to Mr. J. Greenough and Miss Margaret Dargue for the photographs and to Miss J. Hannenberg for translations.

Addendum

Assays have now been performed on 6 mothers carrying hydropic foetuses; in 4 the A.Z. test was positive at 1:100 dilution and in the other 2 at 1:50. None of 16 controls gave a positive test at 1:25 dilution.

References

Acosta-Sison, H. (1956): *Amer. J. Obstet. Gynec.*, **71**, 1279.

Acosta-Sison, H. (1957): *Obstet. Gynec.*, **9**, 233.

Ballantyne, J. W. (1898): *Diseases of the Foetus*. Oliver and Boyd, Edinburgh.

Ballantyne, J. W. (1902): *Manual of Antenatal Pathology and Hygiene*. Green, Edinburgh.

Bastiaanse, M. A. van B., and Mastboom, J. L. (1949): *Gynaecologia, Basel*, **127**, 1.

Bastiaanse, M. A. van B., and Mastboom, J. L. (1950): *in* Ciba Foundation Symposium: *Toxaemias of Pregnancy*. Churchill, London.

Burger, K. (1947): *Zbl. Gynäk.*, **69**, 533.
Burstein, R. B., Herman, T., and Soule, S. D. (1957): *Amer. J. Obstet. Gynec.*, **74**, 85.
Chesley, L. C., Cosgrove, S. A., and Preece, J. (1946): *Amer. J. Obstet. Gynec.*, **52**, 311.
Chown, B. (1954): *Lancet*, **1**, 1213.
Chown, B. (1957): Personal communication.
Dieckmann, W. J. (1952): *The Toxaemias of Pregnancy*, Kimpton, London.
Gemmell, A. A. (1957): Personal communication.
Gemmell, A. A., Logan, W. P. D., and Benjamin, B. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 459.
Goodlin, R. C. (1957): *Obstet. Gynec.*, **10**, 299.
Govan, A. D. T. (1952): *Edinb. med. J.*, **59**, Trans. Edinb. obstet. Soc., p. 35.
Govan, A. D. T., Mukherjee, C. L., Hewitt, J., and Harper, W. F. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 216.
Greenhill, J. P. (1955): *The Principles and Practice of Obstetrics*. Saunders, Philadelphia.
Hellman, L. M., and Hertig, A. T. (1938): *Amer. J. Path.*, **14**, 111.
Henderson, J. L. (1942): *J. Obstet. Gynaec. Brit. Emp.*, **49**, 499.
Herrnberger, K. (1940): *Arch. Gynäk.*, **170**, 287.
Hurst, J. G., Taylor, A., Jr. and Wiener, A. (1946): Blood, **1**, 234.
Jakesch, W. (1878): *Zbl. Gynäk.*, **2**, 619. (Quoted by Ballantyne, 1902.)
Jann, R. (1954): *Arch. Gynäk.*, **184**, 731.
Javert, C. T., and Reiss, C. (1952): *Surg. Gynec. Obstet.*, **94**, 257.
Kaiser, I. H. (1952): *Minnesota Med.*, **35**, 25.
Kloosterman, G. J. (1947): *Over de Polyletaliteit, in Verband met let Vlokkenstrome en de Rhesus factor*. Grafische Kunstinrichting Rotting. Hilversum.
Kloosterman, G. J., and Huidekoper, B. L. (1954): *Gynaecologia, Basel*, **138**, 529.
Landesman, R. (1958): Quoted from *Symposium on Non-Toxaemic Hypertension in Pregnancy*. Edited by Morris and Browne. Churchill, London.
Landesman, R., Douglas, R. G., and Holze, E. (1954): *Amer. J. Obstet. Gynec.*, **68**, 170.
Lermer, A., Villanueva, C., and Tannhauser, S. (1958): *Amer. J. Obstet. Gynec.*, **75**, 203.
Loraine, J. A. (1949a): *Brit. med. J.*, **2**, 1496.
Loraine, J. A. (1949b): *J. Obstet. Gynaec. Brit. Emp.*, **56**, 1051.
Loraine, J. A., and Mathew, G. D. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 542.
Macafee, C. H. G. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 171.
McGaughey, H. S. (1952): *Amer. J. Obstet. Gynec.*, **64**, 1268.
O'Driscoll, D. J., and Lavelle, S. M. (1955): *Lancet*, **2**, 1169.
Page, E. W. (1939): *Amer. J. Obstet. Gynec.*, **37**, 291.
Page, E. W. (1953): *The Hypertensive Toxaemias of Pregnancy*. Thomas, Springfield, Illinois.
Paine, C. G. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 668.
Potter, E. (1947): *Rh—Its Relation to Congenital Haemolytic Disease and Intra-Group Transfusion Reactions*. Yearbook Publishers, Chicago.
Rolleston, H. D. (1910): *Brit. med. J.*, **1**, 846.
Rolleston, H. D. (1920): *Practitioner*, **104**, 1.
Russell, C. S., Paine, C. G., Coyle, M. D., and Dewhurst, C. J. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 648,
Schultheiss-Linder, H. (1942): *Helv. med. acta*, **9**, 810.
Scott, J. S., and Wilson, J. K. (1957): *Lancet*, **2**, 569.
Seeger, G. (1670): *Dec. i. Ann. I. Obs. Lipsiae*, **42**, 132. (Quoted by Ballantyne, 1902.)
Smith, O. W., and Smith, G. van S. (1937): *Amer. J. Obstet. Gynec.*, **33**, 365.
Smith, O. W., and Smith, G. van S. (1940): *Amer. J. Obstet. Gynec.*, **39**, 405.
Sophian, J. (1953): *Toxaemias of Pregnancy*. Butterworth, London.
Theobald, G. W. (1955): *The Pregnancy Toxaemias*. Kimpton, London.
Ten Berge, B. S., and van Assen, F. J. J. (1947): *Nederl. Tijdschr. Geneesk.*, **91**, 1229.
Velez Orozco, C., Guerrero, C. D., and Marvan, A. (1950): *Ginec. Obstet. Mex.*, **5**, 7.
Walker, W., Murray, S., and Russell, J. K. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 577.
Wislocki, G. B., Dempsey, E. W., and Fawcett, D. W. (1948): *Obstet. Gynec. Surv.*, **3**, 604.
Zsigmond, Z. (1941): *Zbl. Gynäk.*, **65**, 1258.

THECAL AND ALLIED REACTIONS IN EPITHELIAL OVARIAN TUMOURS

BY

P. E. HUGHESDON, M.D.

Assistant

Department of Morbid Anatomy, University College Hospital Medical School, London

THE word "theca" is Latin for "sheath"; but, as ordinarily used, it is understood to designate either that specialized part of the ovarian stroma that ensheathes the granulosal part of a Graafian follicle, or its homologue in a tumour. From this use it has acquired also a derived meaning; for the term "thecal reaction" has often been applied to any local collection of cells which resemble those of the theca interna—more especially after luteinization—whether they ensheathe anything or not. This extension could be misleading, if inferences as to function are transferred from one type of thecal reaction to the other; for the behaviour of cells is likely to depend in part on where they are. The object of the present article is to describe the rare occurrence of thecal reactions in the first sense in several quite ordinary epithelial ovarian tumours.

MATERIALS AND METHODS

The material consists of 10 primary ovarian carcinomas seen in the years 1955 and 1956, all of them of various banal patterns to be described. In the same period the total number of primary ovarian carcinomas operated on was 27; but this high incidence of thecal reactions was probably exceptional, for none was seen in the 15 cases of 1957. All the material was fixed in 10 per cent formalin, and an average of 4 paraffin blocks made from each tumour. Sections were stained with Harris's haematoxylin and eosin, Mallory's phosphotungstic acid haematoxylin, and by a modified Gomori reticulum impregnation. Frozen blocks were made in the 6 cases in which material from the original specimen was still available; and from these, sections were stained with Sudan IV and Harris's haematoxylin, whilst lightly stained, undifferentiated haematoxylin sections were examined with the polarizer.

FINDINGS

It is convenient to describe 2 typical cases, and then to give the overall findings in summary.

Case 1. Mrs. H.G., aged 47, had had abdominal distension and a bearing-down pain for 10 days. Her periods had been regular (4–5/27–30) since the menarche at 12, but her last period had been prolonged (9 days) till the time of admission. She had had 1 child (aged 11), no abortions, and no noteworthy past history. On examination, the only abnormality was a soft mass in the pouch of Douglas. At laparotomy (18th October, 1955—Mr. James Elstub), there was much clear fluid in the abdomen; and the left ovary was replaced by an orange-sized cyst, gelatinous and haemorrhagic in places, with several ruptured locules. The sigmoid was adherent to the back of the left broad ligament: the uterus and right ovary seemed normal. Panhysterectomy was performed. Convalescence was complicated by ileus, and by a fever (responding to terramycin) attributed to a pleuro-pneumonia-like organism cultivated from high vaginal swabs and from the blood. The patient had a course of radiotherapy, and was well and free from recurrence 22 months later.

The excised object consisted of a complete uterus ($9\times6\times4$ cm.), with an anterior intramural fibroid 7 mm. in diameter and several mucosal polypi; normal tubes; a normal right ovary ($3\times2\frac{1}{2}\times1\frac{1}{2}$ cm.); and a left ovarian tumour ($11\times8\times7$ cm.). The last was about three-quarters solid, with a hilar ovarian remnant from which fibrous septa extended inwards to enclose various locules, all filled upwards of 50

per cent by soft papillary or solid rolled-up growth. About two-fifths of the surface had no wall, carcinomatous tissue having been exposed by peeling the tumour off its surroundings. The wall (where present) was mostly thin (up to 1 mm.), but expanding to 7 mm. at the hilus.

Sections of the right ovary showed nothing of note. The uterine cavity contained some loose fragments of adenocarcinoma (similar in pattern to that of the left ovary), and a small carcinomatous polyp with an abrupt edge (and so presumed to be an implant). The uterine mucosa was otherwise of proliferative phase type. The left tumour (from which 8 blocks and 960 serials were cut) showed a substantial hilar plaque of ovarian remnant, consisting (on section) of an irregular pale crescent of medulla and an outer dark rim of cortex. From this plaque septa extended into the tumour, and a few detached islands of ovarian cortical tissue (with primordial follicles) were found a short distance off within these. The growth itself was an adenocarcinoma of endometrial pattern—that is, it showed various adenoid, adeno-papillary, cribriform, and occasionally non-cornifying squamous patterns, similar to those of a carcinoma of the body of the uterus. Wrapped round these various epithelial patterns was a particular mantle of connective tissue, which in some places had a loose mesenchymal character (resembling endometrial stroma), and in others was more condensed and showed reactions of theca-lutein type. Figure 2 shows a wedge of close-packed, pale, boxy theca-lutein cells at the base of a septum between two adenocarcinomatous spaces. Figure 3 shows another area, where the growth is more solid and the ensheathing theca-lutein cells are more eosinophil; whilst Figure 4 shows the relatively condensed, pericellular, cribriform reticulum associated with the last in a neighbouring section. In other areas the thecal cells were smaller, often condensed into clusters or trains lying in a halo-like zone of loosened tissue, and often interspersed with bundles of immature smooth muscle. On the side of the ovarian remnant (where it bordered the medulla) this tissue often blended with a narrow seam of dark ovarian-cortex-like tissue (itself similarly hatched with immature smooth muscle); and, at one point just inside the junction of the two, a single very early ripening follicle was found. In frozen sections, foci of sudanophil droplets were seen in thecal areas corresponding to those just described, and there was also scanty doubly refractile intra-cellular fat.

Case 2. Mrs. F.E., aged 56, had had abdominal pain and distension for 10 weeks. She had had the menopause, with flooding, 3 years previously; 2 children; no abortions; and no noteworthy past history. At laparotomy (2nd December, 1955—Mr. G. Clare), a ruptured left-sided ovarian cyst was found, the other pelvic organs appearing normal. Panhysterectomy was performed, and convalescence was uneventful save for considerable psychic depression. The patient subsequently had radiotherapy; and was well and free from recurrence 16 months later. The excised object consisted of a complete uterus (7×6×4 cm.) with a small fundal endometrial polypus and a seedling intramural fibroid, normal tubes, a calcified fibroid (1 cm. in diameter) in the right mesosalpinx, and a seemingly normal right ovary: the left ovary was replaced by a unilocular cyst 13 cm. in diameter. This showed at the hilus a solid, partly papillary mass, about 5 cm. in diameter, lying in the wall and projecting both inwards and outwards; and (a few cm. away) a comparably situated fibrous knob, 2 cm. in diameter.

Sections of the uterus showed an endometrial polypus, associated with a general cystic hyperplasia: this looked active, and showed occasional mitoses. The portio squamous epithelium was notably thick and pale. The right ovary showed very early lesions of endometriosis, as did the hilar ovarian remnant on the left. The tumour proved to be a carcinoma of mesonephric type: that is, it varied from a solid, clear-celled hypernephroid pattern, with thin connective tissue septa, through various rather pale adenoid and adeno-papillary—occasionally pseudo-glomerular—types of structure, with plentiful intervening cellular connective tissue, to microcystic spaces lined by hobnail or endothelioid epithelium, lying in denser and more inactive fibrous connective tissue. Parts of the second pattern showed a distinct stromal mantle, which appeared in places to blend with the epithelial structures, as in a mixed mesodermal tumour: this impression of blending was dispelled by a reticulum impregnation, which showed sharp edges between the two elements throughout. In other parts, adenoid and adeno-papillary structures lay about at random in a sea of cellular connective tissue, and small

nests of lutein cells were commonly present in relation to them: Figure 5 shows an example. The tissue loosening surrounding the lutein nest is apparent; and Figure 6—a corresponding area from a nearby section—shows this to be associated not only with oedema, but also with fibrillary dissociation.

Collected data about all 10 cases may now be given. The ages were 36, 39, 40, 42, 47, 48, 55, 56, 57 and 60: the last four were post-menopausal (though the qualifying statement must be made that the penultimate patient listed had had a vaginal hysterectomy 16 years previously). Parity varied from 0 to 4, and showed no special tendency. None of the six pre-menopausal cases had any striking menstrual abnormality. One patient, aged 36, had some coarseness of her hair which had been quite gradually increasing, a growth of hair on her upper lip which worried her, a male distribution of pubic hair, and rather a large clitoris: no other data are available as to the duration of this mild virilism. As it was not associated with any menstrual abnormality, it may well have been constitutional and unrelated to her tumour: the histology of part of this is seen in Figure 9, though other parts resembled Figure 7. No other patient is known to have had any signs of virilism. The uterus was available only in 6 cases. Two of these showed a somewhat atypical proliferative phase: one of them is Case 1, and the other was not available until 29 days after removal of the ovarian carcinoma. The other 4 showed cystic hyperplasia, of typical and florid pattern, with active-looking cells but scanty actual mitoses—Figure 10 shows an example: two of these were post-menopausal (3 and 7 years). No post-menopausal case had any vaginal bleeding, with or without cystic hyperplasia. As to outcome, 5 remained free from recurrence for 13, 16, 18, 22 and 25 months; and 5 had known or presumptive recurrences in 1, 6, 6, 7 and 9 months (3 of these having died). The largest tumour measured $20\times15\times5$ cm., and the smallest $6\frac{1}{2}\times6\times3\frac{1}{2}$ cm., whilst most were about 10–12 cm. in diameter: their gross appearance did not differ from the general run of ovarian carcinomas. Two patients had bilateral tumours and 8 unilateral; but of the latter, 2 had previously had benign (or presumptively benign) tumours removed from the contralateral ovary. In histological pattern, 3 of the tumours were dark-celled serous papillary to anaplastic carcinomas; 3 were pseudomucinous adenocarcinomas; 1 was a mesonephric carcinoma; and 3 were quasi-endometrial carcinomas (similar to Case 1, and associated in one case with endometrial cysts of both ovaries): thus, a thecal reaction was not especially associated with any particular pattern.

The forms taken by the reaction varied. The most elementary is shown in Figure 1, where there is merely a condensation of cellular connective tissue in the region bordering the epithelial part of the tumour. This blends with the adjacent ovarian connective tissue below (and presumably derives from it), but presents a sharp border to it above (as if segregating into a distinct layer). In places within the tumour (another quasi-endometrial carcinoma) it loosened up to have some resemblance to endometrial stroma. Alone of the 10 cases this tumour showed no luteinization in this stromal mantle, but there were foci of small sudanophil droplets. Such a mantle was present in all the tumours—sometimes in relation only to a small part; and within this, foci of little lutein cells were seen. The most developed form of this reaction is shown in Figures 2–4: here virtually the whole mantle has luteinized, so as to surround the epithelial structures of the tumour with a theca-lutein pavement resembling (but exaggerating) that round a follicle. More usually the lutein cells formed little nests (Figs. 5, 7–9, 11, 12), and quite commonly these were associated with conspicuous local tissue loosening: examples of this phenomenon were noted in 9 cases. The smaller collections of lutein cells often formed little trains or agglutinated clusters, surrounded by a halo of tissue loosening (Fig. 8, above and below respectively). Reticulum impregnation of these areas showed both oedema and fibrillary dissociation (as in Fig. 6). The small lutein cells in these clusters tended to lose the rounded or polygonal form of Figures 2 and 3, becoming stellate, with cytoplasmic processes: Figures 5, 7, 8 and 9 progressively indicate this change of form (which has its analogue in the different

FIG. 1

Partly folded, partly stratified epithelial lining of locule of quasi-endometrial carcinoma, bordered by condensed stromal layer which blends with adjacent tissue below but shows sharp margin above. H. & E. ×70.

FIG. 2

Case 1. Wedge-shaped base of septum between two gland spaces in another quasi-endometrial carcinoma, showing a nest of rather pale small lutein cells with rounded vesicular nuclei. H. & E. ×200.

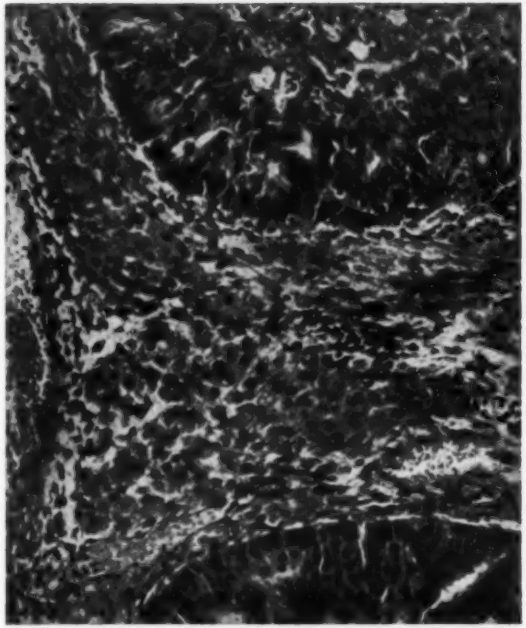


FIG. 3

Case 1. A similarly placed, nearby part of the tumour, showing folded and re-duplicated epithelium surrounding granular debris above, and bordered by a nest of eosinophil theca-lutein cells similar to those of a ripening follicle. H. & E. ×170.

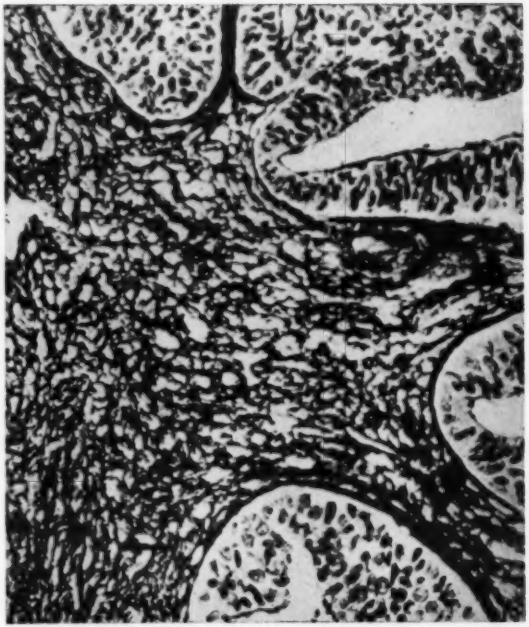


FIG. 4

Case 1. Similar area from nearby section, showing cribriform pericellular reticulum in thecal region. Modified Gomori. ×185.

FIG. 5

Case 2. Mesonephric carcinoma, showing arcuate string of small acini composed of pale cubical epithelium. Within its concavity lies a nest of small lutein cells, surrounded by loosened connective tissue. H. & E. ×175.

FIG. 6

Case 2. Corresponding region from nearby section, with central loosened area showing oedema, together with dissociation of fibres compared with those running down either side. Modified Gomori. ×220.

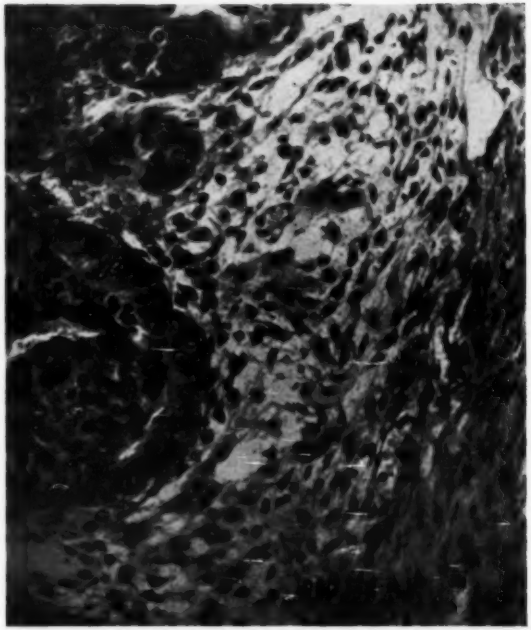


FIG. 7

Part of an anaplastic serous carcinoma, showing epithelium on the left; bordered by a band of loose connective tissue down the middle, in which small polygonal and stellate lutein cells form a cellular reticulum with unluteinized connective tissue cells, with transitional forms; and a band of immature smooth muscle to the right. H. & E. ×230.

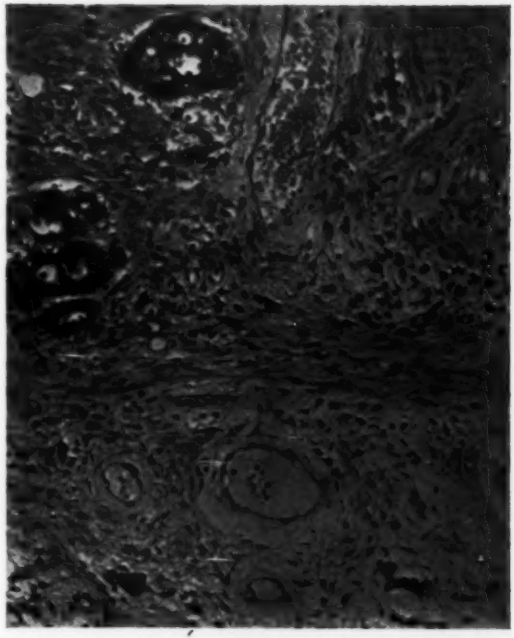


FIG. 8

Part of another similar tumour, showing poorly formed epithelial gland spaces at top left, some immature smooth muscle—notably in central transverse band, and some loosened connective tissue containing a few small lutein cells. These can be seen agglutinated into two irregular clusters below and a cell train above. H. & E. ×120.

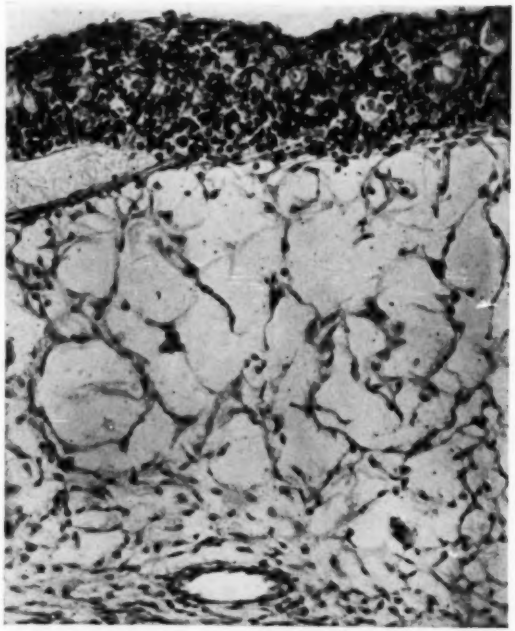


FIG. 9

Part of a quasi-endometrial carcinoma, with anaplastic stratified epithelial layer above and oedematous loose connective tissue septum below. In the meshes of the latter are seen a few small dusky agglutinated theca cell clusters. H. & E. ×130.

FIG. 10

Part of uterine wall showing cystic endometrial hyperplasia of florid pattern associated with an anaplastic serous carcinoma with a septal thecal reaction in a woman of 60. H. & E. ×30.

FIG. 11

Part of a pseudomucinous adenocarcinoma: in the concavity of the large main gland space is an irregularly crescentic dense nest of small lutein cells. H. & E. ×185.

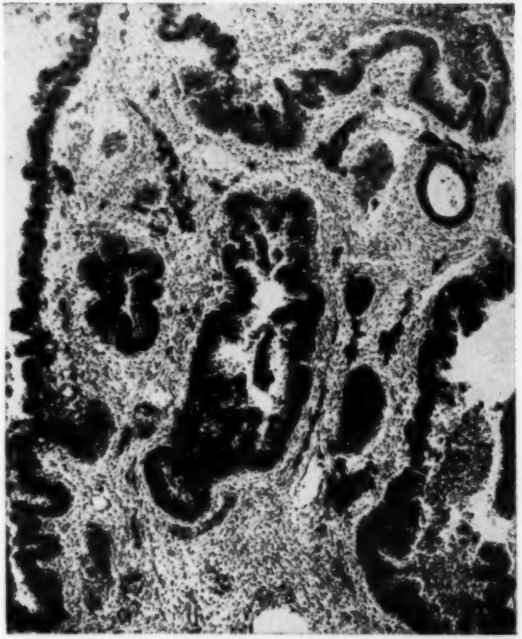


FIG. 12

Another pseudomucinous adenocarcinoma, stained to show fat. Various epithelial spaces with dark wavy borders are evident, together with three cut tangentially (to the right of centre) appearing small, dark and ovoid. In the intervening connective tissue septa are seen some slightly darker streaks and amorphous nests of lipoid-containing cells. Sudan IV and haematoxylin. ×50.

appearances of decidual cells in compact and in loosened areas). A common intermediate type (both with and without processes) looked like an atypical plasma cell with eosinophil cytoplasm. The extreme case is shown in Figure 9, where there is maximal reduction of the perinuclear cytoplasm: the corresponding reticulum impregnation showed (as might be expected in relation to this figure) a filigree network surrounding fibril-free locules of gross oedema. In the 3 pseudomucinous carcinomas the common form seemed to be condensed theca-lutein nests and leashes, of which an example is shown in Figure 11.

Sudanophil lipoid was found in varying quantity (in areas corresponding to the situation of the theca cells in paraffin sections) in all 6 cases with available unblocked material: these included all the cases here figured except Case 2 (Figs. 5 and 6). A single and typical figure from a pseudomucinous adenocarcinoma is shown in Figure 12. In the stroma separating the epithelial spaces (three of which, to the right of centre, have been cut tangentially) are seen dark formless aggregates of sudanophil cells, five of them noticeably streaked out. Doubly refractile lipoid was seen plentifully in one case (corresponding to Fig. 7), scantily in another, and very scantily in the remaining 4. Smooth muscle was present in the ensheathing mantle of stroma in 9 of the 10 cases: in none was it abundant, and in all the fibres were mostly small, slender, and immature. Their identification as muscle cells was confined in each instance (including that shown in Fig. 10) by the demonstration of characteristic longitudinal myofibrils with phosphotungstic acid haematoxylin.

Discussion

There are 4 matters for discussion, namely, the literature; the possibility of steroid hormone production by these tumours, since it is the normal function of follicular theca to produce oestrogens (Burrows, 1949) and possibly androgens (Shippel, 1950); the tissue loosening, since it is precisely by such means that the theca interna (by means of the theca cone) loosens the tissues of the ovarian surface and permits follicle rupture (Shaw, 1927; Harrison, 1948); and finally the general diagnostic significance of a thecal reaction in a tumour.

(1) *The Literature.* The phenomenon described must be distinguished from two others which are rather analogous. The ovarian cortical hyperplasia of later life described by Woll, Hertig, Smith and Johnson (1948) is often associated with foci of stromal luteinization; and this may be found in the ovarian remnant attached to, or included in, any ovarian tumour. I have seen and heard of instances of this, but know of none published. In addition, hilus cell hyperplasia has been noted or described in association with several ovarian tumours, e.g., ordinary epithelial tumours (Neumann, 1927), Brenner (Jennings and Irwin, 1956), dysgerminoma (Usizima, 1956), and thecoma (Hughesdon, 1958). The finding of lutein cell clusters in either the ovarian remnant or the mesovarium is clearly distinct from their recognition in a specific tumour mantle; and the transference of endocrine or other inferences from one to the other would not be justifiable.

The development in ovarian carcinoma of a cellular stroma (similar to my Fig. 1, and sometimes thick enough to suggest a sarcoma) has occasionally been noted, e.g., Pfannenstiel (1898) and Geist (1942). It may be that some ovarian "carcino-sarcomata" have been misidentifications of this phenomenon, but I do not know a published case which distinctly suggests this. More recently, Fisher, Krieger and Skirpan (1955) have described this condensed stromal layer as a "desmoplastic reaction", and considered it to be an indication of malignancy in serous but not in pseudomucinous tumours.

Definite theca-lutein change in the stroma of an ordinary ovarian tumour has only a brief relevant literature. Bettinger and Jacobs (1946) described a pseudomucinous cystadenoma, with areas of *adenoma malignum*, containing cells like those of a luteinized theca interna in the stroma: it was associated with a mild virilism which recovered after its removal. McKay, Robinson and Hertig (1949) found, in a single ovarian carcinoma, histochemically reactive material (i.e., presumptive steroids) both in the tumour cells and in the connective tissue septa. Shippel's (1950) tumour, associated with amenorrhoea and a hypoplastic endometrium,

seems rather to resemble my Case 2. Turunen (1955) described 8 Krukenberg tumours associated with cystic endometrial hyperplasia, and in 1 case with an excessive urinary output of oestrogens: with Sudan III staining "cells containing red-staining lipoids, which were obviously theca cells, were found in the connective tissue of all the tumours, in greater or smaller amounts" (p. 54), and oestrogen production was attributed to these. Bamforth, Dempster and Garland (1956, Case 1) described as a malignant Brenner tumour an adenocarcinoma with no self-evident claim to this title: its acini were surrounded by groups of fat-containing pale cells, which might well have been thecal reaction. Nothing suggesting a hormonal effect is mentioned. Recently, Scully and Morris (1957) have remarked on seeing "a small number of cystadenomas, Brenner tumours and primary adenocarcinomas of the ovary whose stroma has simulated a theca cell tumour and has contained cells having the morphology of lutein cells". An example is mentioned and figured of an adenocarcinoma with such a reaction, in a woman of 74: it was associated with endometrial hyperplasia and vaginal bleeding.

(2) *Steroid Hormone Production.* My only hirsute case was clearly rather dubious; but the one cited of Bettinger and Jacobs is convincing, and suggests a possible rational interpretation of occasional androgen production by ordinary epithelial tumours. A number of early cases of this association were reviewed by Halban (1925), though several of these were evidently arrhenoblastomas. Büttner (1932, Case 2) described a Krukenberg tumour (with a gastric primary) associated with virilism during pregnancy: this recovered following removal of the tumour shortly after delivery. This coincidence with pregnancy makes interpretation uncertain: on the other hand it makes it more likely that a thecal reaction (of which there is no mention) was present in the proliferating stroma of the tumour. Correa da Costa (1938) described a case of virilism associated with an ovarian tumour of which the histology showed pseudomucinous cystadenoma and lymphangioma.

The strong possibility of oestrogen production by ordinary tumours with thecal reactions is indicated by the several cases described and cited with associated cystic endometrial hyperplasia. Watts and Adair (1941) found oestrogens in the fluid of various ordinary ovarian cysts, both benign and malignant. It has always been debatable whether ordinary ovarian tumours (more especially carcinomas) can produce abnormal uterine bleeding as a specific and proper symptom. Bayly and Greene (1956) have recently reviewed the matter: they found that only rarely was there no explanation of such bleeding in the associated pelvic pathology; and that 22 per cent of post-menopausal women with ovarian tumours had cystic endometrial hyperplasia, which compares with the figure of 19·2 per cent of Novak and Richardson (1941) in post-menopausal women with no gross pelvic pathology. However, the slightness of the difference is what might be expected if, in the bulk of cases, the association is fortuitous; whilst in a small minority with thecal reactions it is of causal significance. The study of large numbers will tend to blanket out this point; and the same applies *mutatis mutandis* to vaginal bleeding. This did not occur in either of my 2 post-menopausal cases with cystic hyperplasia, though doubtless it would have done so in time.

(3) *The Tissue Loosening.* In assessing this finding (Figs. 5–9) it should not be forgotten that thecal tissue has an external as well as an internal secretory function. The relation of theca to granulosa is analogous to that of muscle to an epithelial duct, but more ambiguous; since the theca not only encloses and retains the follicular fluid, but also (in due course) does the opposite—by loosening the ovarian surface and permitting rupture of the follicle and escape of its contents. It is likely that the loosening abilities of theca cells are not confined to the theca cone; for the tissue surrounding the theca interna of a ripening follicle is commonly rather loose (which probably helps to maintain a rounded contour). Also, it is not rare to see marked loosening round the surviving peripheral thecal layer of an established—or even defunct—corpus luteum. Amongst the functioning tumours, small collections of theca-lutein-type cells lying in a zone of tissue loosening have been figured in arrhenoblastoma by Taylor,

Wolfermann and Krock (1933, Fig. 8), less strikingly by Schiller (1936, Fig. 5), and in minor degrees by a few other authors. I know of no comparable instance in theco-granulosal tumours, where discrete collections of such cells are less common.

A speculative answer can be given as to how this effect is mediated. Of substances known to induce tissue loosening, the most likely agent is relaxin or a similar substance (for a general review of which, see Hisaw and Zarrow, 1950). Not only is its production widespread in the female genital tract (e.g., ovary, uterus, placenta), but also it induces (in the cervix and symphysis of oestrogen-primed mice) a fibrillary dissociation similar to that here described—though without the same local pooling of tissue fluid (Storey, 1957). That the theca interna produces relaxin is suggested by some observations of Mossman (1937) on the pocket gopher: in this animal a quite prodigious and exceptional development of the theca-lutein layer round a ripening follicle is associated with symphyseal separation during pro-oestrus and oestrus. Now relaxin is a polypeptide, and there seems no reason why a cell producing it should necessarily be a lutein cell; and the same would apply *mutatis mutandis* to any non-lipoid tissue-loosening substance. The foamy or granular lutein cell cytoplasm (found in all cells producing steroid hormone) is no more than a universal cell reaction to the handling of lipoids: a histiocyte in a lipo-granulomatous reaction looks much the same. It so happens that the two offices are (probably) combined in theca-lutein cells. The type of stromal appearance shown in Figure 9 (but without lutein cells) is a very common one in "serous" tumours of all kinds, benign and malignant. It would be a misuse of terms to describe it as a "thecal reaction": yet it may well be allied, in that it exercises one function (tissue loosening) but not the other (steroid hormone production) proper to theca.

A unitary view of all the phenomena described would be that sometimes the ovary treats an expanding tumour as if it were a ripening follicle. Probably a thecal reaction is a specific response of actively proliferating ovarian stroma to being stretched (whilst the smooth muscle formation also noted is a non-specific one). This may result in steroid hormone production and/or in local tissue loosening; and the latter is clearly (for the patient) a most inexpedient happening round an expanding malignant tumour. I have however no evidence as yet that this loosening is of importance in producing the common technical inoperability of these tumours, and have found (in the present series and elsewhere) that ovarian carcinomas break through a pre-existing capsule as a result of simple necrosis or of a local patch of *pseudomyxoma ovarii*—which latter, in the abstract, somewhat resembles in pattern the loosened areas described. Other carcinomas are inoperable because they become malignant too early to acquire a complete ovarian capsule, and before they entirely leave the ovarian surface. They remain (at least in part) on, rather than in, the ovary which is attempting to enfold them; so that their structure is rather like that of an endometrial cyst (Hughesdon, 1957). However, the tissue corresponding to the "inner cortex" of an endometrial cyst gets irregularly scalloped, broken up, and carried into the septa of the tumour, as was adumbrated in the description of Case 1. In this case the dislocated fragments of inner cortex, folded round the gland spaces of the tumour, responded by proliferating and producing the thecal mantle described; as was evidenced by blending of this mantle with presumptive inner cortical remains and the presence in it of an early ripening follicle at one point. (This architectural feature is at present being investigated.) To return: the small number and short follow-up of the present series permits no definite inference as to the effect of a thecal reaction on prognosis; but it does not suggest a dramatic difference either way from the general run of ovarian carcinomas.

(4) *The Diagnostic Significance of Thecal Reactions.* The four histological growth patterns occurring in this series—pseudomucinous, quasi-endometrial, dark-celled serous papillary, and mesonephric—are (in my view) the four basic ones of primary ovarian carcinoma. By "mesonephric" is meant a tumour similar to those described by Novak, Woodruff and Novak (1954) and Stowe (1955), the grounds of the identification being the resemblance to extra-

ovarian carcinomas judged to be mesonephric by their site—and not a resemblance to mesonephros. The other patterns I believe to correspond respectively to primary carcinomas of the endocervix, endometrium and tube, and to reflect the principle expounded elsewhere (Hughesdon and Fraser, 1953) that primary non-teratoid ovarian tumours base their patterns on those of the tissues (of either sex) derived from intermediate mesoderm, together with their embryonic phases and their tumours. Be this as it may, the present tumour patterns were both ordinary and varied, and not at all of a nature in which a thecal reaction would be a biologically rational piece of tissue correlation.

It follows that the occurrence of a thecal reaction as such does not in itself identify a tumour as one of the "special", functional or gonadal variety, either in the individual instance or generally. It is likely that many published and unpublished tumours have been misidentified on this ground, and 2 possible instances have (with all due reserve) been cited. To move to the general: thecal reactions in Brenner tumours have been described or noted by Teoh (1953), Biggart and Macafee (1955), Mackinlay (1956), and Scully and Morris (1957). Teoh's inference from this that Brenner tumours are a form of granulosal tumour is clearly invalid, though his other arguments are not affected. On the other hand the converse possibility is also raised—that the distinction between the gonadal and non-gonadal tumours (though usually they are widely different) may not be absolute, and that occasional truly intermediate forms may occur. Willis (1948) states that in bitches papillary epithelial and granulosal tumours are not sharply distinguished; but in these animals the granulosa normally forms from epithelial cords of surface origin (Mossman, 1952), so that the finding may not be transferable to women. To consider the point however—one tumour in my series, of serous papillary to anaplastic structure, showed sharply defined dark epithelial trabeculae with included adenoid spaces: the pattern was analogous to that of a microfolliculoid granulosal tumour, and has often been confused with it in the literature. It occurred in a woman of 60, and was associated with a stromal thecal reaction and with the endometrium shown in Figure 10: did the resemblance possess therefore a deeper significance than accidental imitation? It is difficult to resolve this question into one of fact: it can be said, however, that this pattern showed transitions to typical serous papillary areas, and did not show them to stromal or thecal areas (which relation can usually be found with care in a granulosal tumour). A tumour combining the features of arrhenoblastoma and adenocarcinoma has been described by Dubrauszky (1948), but the pictures are not very clear: some related instances have earlier been reviewed (Hughesdon and Fraser, 1953).

Summary

(1) Ten ovarian carcinomas are described, in which the stroma showed a thecal reaction. One case was associated with a mild virilism which was probably coincidental. Four out of 6 cases in which the uterus was available showed cystic endometrial hyperplasia. Nine cases showed local areas of tissue loosening associated with groups of theca-lutein cells.

(2) The literature of certainly and possibly related cases (which include some secondary tumours) is reviewed. There is evidence that a stromal thecal reaction in a variety of ordinary epithelial tumours may produce an oestrogenic effect, and very occasionally an androgenic effect.

(3) It is suggested that ovarian tissue may sometimes treat an expanding tumour as if it were a ripening follicle. The tissue loosening may relate to that induced by the theca cone before follicle rupture. The possible unfortunate consequence of this in ovarian carcinoma is discussed.

(4) It is clear that one cannot deduce from the presence of a stromal thecal reaction that one has to do with a granulosal cell tumour, arrhenoblastoma, or any other special tumour of gonadal type. The possible occurrence of forms intermediate between these and the banal adenoid and papillary tumours is discussed.

I am much indebted to Mr. Aleck Bourne, Mr. A. H. Charles, and Mr. J. D. S. Flew for

providing me with data about private patients, and for permission to make use of it; to Mr. A. S. Bligh for the photographs; and to Sir Roy Cameron, F.R.S., for his interest.

References

Bamforth, J., Dempster, K. R., and Garland, G. W. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 344.

Bayly, N. A., and Greene, R. R. (1956): *Amer. J. Obstet. Gynec.*, **72**, 143.

Bettinger, H. F., and Jacobs, H. (1946): *Med. J. Aust.*, **1**, 10.

Biggart, J. H., and Macafee, C. H. G. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 829.

Büttner, A. (1932): *Virchows Arch.*, **287**, 452.

Burrows, H. (1949): *Biological Actions of Sex Hormones.* 2nd edition. Cambridge University Press, London. pp. 298–300.

Correa da Costa, C. (1938): *Rev. Obstet. Ginec. (Rio de Janeiro)*, **32**, 3.

Dubrauszky, V. (1948): *Z. Geburts. Gynäk.*, **130**, 38.

Fisher, E. R., Krieger, J. S., and Skirpan, P. J. (1955): *Cancer*, **8**, 437.

Geist, S. H. (1942): *Ovarian Tumors.* Hoeber, New York. pp. 207, 213.

Halban, J. (1925): *Z. Konst. Lehre*, **11**, 294.

Harrison, R. J. (1948): *J. Anat.*, **82**, 21.

Hisaw, F. L., and Zarrow, M. X. (1950): *Vitam. and Horm.*, **8**, 151.

Hughesdon, P. E. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 481.

Hughesdon, P. E. (1958): *J. Obstet. Gynaec. Brit. Emp.*, **65**, 540.

Hughesdon, P. E., and Fraser, I. T. (1953): *Acta obstet. gynec. scand.*, **32**, Suppl. 4.

Jennings, R. C., and Irwin, W. T. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 914.

McKay, D. G., Robinson, D., and Hertig, A. T. (1949): *Amer. J. Obstet. Gynec.*, **58**, 625.

Mackinlay, C. J. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 58.

Mossman, H. W. (1937): *Amer. J. Anat.*, **61**, 289.

Mossman, H. W. (1952): *in* E. T. Engle (ed.): *Studies on Testis and Ovary, Eggs and Sperm.* Thomas, Springfield, Illinois. Chapter 12.

Neumann, H. O. (1927): *Virchows Arch.*, **263**, 274.

Novak, E., and Richardson, E. H. (1941): *Amer. J. Obstet. Gynec.*, **42**, 564.

Novak, E., Woodruff, J. D., and Novak, E. R. (1954): *Amer. J. Obstet. Gynec.*, **68**, 1222.

Pfannenstiel, J. (1898): *in* Veit, J.: *Handbuch der Gynäkologie.* Vol. 3. Bergmann, Wiesbaden. p. 352.

Schiller, W. (1936): *Arch. Gynäk.*, **160**, 344.

Scully, R. E., and Morris, J. McL. (1957): *in* Meigs, J. V., and Sturgis, S. H.: *Progress in Gynecology.* Vol. 3. Grune and Stratton, New York. p. 31.

Shaw, W. (1927): *J. Obstet. Gynaec. Brit. Emp.*, **34**, 469.

Shippel, S. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 362, 557.

Storey, E. (1957): *J. Path. Bact.*, **74**, 147.

Stowe, L. M. (1955): *Cancer*, **8**, 446.

Taylor, J. M., Wolfermann, S. J., and Krock, F. (1933): *Surg. Gynec. Obstet.*, **56**, 1040.

Teoh, T. B. (1953): *J. Path. Bact.*, **66**, 441.

Turunen, A. (1955): *Acta endocr., Copenhagen*, **20**, 50.

Usizima, H. (1956): *Cancer*, **9**, 736.

Watts, R. H., and Adair, F. L. (1941): *Cancer Res.*, **1**, 638.

Willis, R. A. (1948): *Pathology of Tumours.* Butterworth, London. Chapter 29.

Woll, E., Hertig, A. T., Smith, G. van S., and Johnson, L. C. (1948): *Amer. J. Obstet. Gynec.*, **56**, 617.

LIPOID MASCULINIZING TUMOURS OF THE OVARY

With a Report of a Case

BY

D. H. LEES, F.R.C.S.(Ed.), M.R.C.O.G.

AND

C. G. PAINE, M.D.

The Jessop Hospital for Women, Sheffield

MASCULINIZATION associated with ovarian tumours is due most commonly to arrhenoblastomata, but during the past forty years there has been described a series of cases of masculinization due to the presence of ovarian tumours bearing a close histological resemblance to adrenal cortical tissue. These tumours are rare and only 35 have been described.

Because of our imperfect knowledge of their origin and relationships it is convenient to use the general designation of virilizing lipoid cell tumours as suggested by Barzilai (1943). Iverson (1947) points out that the reference to their lipoid character differentiates them from arrhenoblastomata and the virilizing potential distinguishes them from the luteinizing granulosa cell tumours, but adds that there is certainly some common ground histologically between all three groups and that differential clinical features are not at all absolute. This accords with the general view that tumour development in the ovary is still imperfectly understood.

Macroscopically these lipoid ovarian tumours appear as spherical masses surrounded by a rind of atrophic and fibrous ovarian cortical stroma. There is considerable variation in size, the smallest being minute nodules, the larger seldom exceeding 6 inches in diameter. The most striking naked eye feature is their bright yellow colour, which strongly resembles that of the adrenal cortex or the corpus luteum. Haemorrhage into the tumour may modify its appearance considerably.

Microscopically their appearance is characteristic; they consist of masses or columns of large vacuolated polyhedral cells, imitating in structure the adrenal cortex. The cell content is largely neutral fat, but some anisotropic lipoid material is usually present. In several cases attention has been drawn to the very high glycogen content of these tumours. Fuchsinophil granules (Broster and Vines, 1933) which are characteristic of adrenal cortical masculinizing tumours, are a rare finding. Of the cases studied, in only 2 have metastases been recorded (Rottino and McGrath, 1939; Burkett and Abell, 1944).

Clinically these tumours cause little local upset since they are small and in only one recorded case (Rottino and McGrath, 1939) was there a degree of ascites; and in that case secondaries developed subsequently. This absence of ascites is noteworthy because the present case was very different in this respect. The main clinical features are due to the hormonal activity of the tumours. Amenorrhoea, mammary atrophy, general masculine habitus, together with hirsutes of the trunk and extremities, beard growth and baldness are usual in such cases. The development of these changes is gradual and there is a long time interval between the onset of symptoms and operative

treatment. In some of the cases manifestations more commonly associated with the adrenogenital syndrome are present. These include hypertension, polycythaemia, obesity, diabetes and a raised metabolic rate.

The urinary steroid metabolic products have been studied in some of the cases but the results are of limited clinical application. Generally speaking there is an increase in androgen excretion, with the 17-ketosteroid output raised to about the level one finds in arrhenoblastoma, and not at all like the high figure found in adrenal cortical masculinizing lesions. Searle, Haines and Baker (1948) did record a case where the 17-ketosteroid figure was very high but that patient was pregnant and subsequent estimates showed that it fell steeply after delivery to about the moderate elevation previously mentioned.

Case Report

Mrs. G.W., a housewife, aged 47, attended the Gynaecological Clinic of the Jessop Hospital on 25th May, 1956. She complained of abdominal enlargement which had developed gradually over 7 years and increased more rapidly in the last 6 months. Coincident with this she had noted her arms and legs becoming thinner. She found it difficult to walk because of the large abdomen and she experienced increasing breathlessness on exertion. For about 17 years she had been worried by the growth of coarse hair on her face, chest, legs and abdomen, and for several years had to shave the beard area daily. She was also developing baldness of a male type at the same time.

She said her general health had been reasonably good and she was quite active despite the large abdomen. In support of this she told us that she had decorated two rooms in her home before coming to hospital.

Menstrual History. Menstruation commenced at the age of 14 and she had a regular 28 day cycle with a 5–6 day loss until aged 30. Her periods ceased abruptly then and she had no further loss over the next 17 years.

Obstetric History. She had one stillborn child following a difficult breech delivery. There was a moderate postpartum haemorrhage. This was 20 years previously and 3 years before menstruation finally ceased.

Examination

The immediate obvious feature was a huge abdominal swelling and the rest of the body was thin and shrunken by comparison (Fig. 1).

Despite first appearances her general condition was fair. Temperature and pulse were normal, her colour was reasonably good but the blood pressure was raised to 150/100. She weighed 198 pounds.

The scalp hair was thin, with recession at the temples and near complete baldness over the parietal regions. There was coarse hair on the face and it was obvious that she shaved frequently. There was thick coarse hair on the arms and legs and straggly hairs on the breasts and lower abdomen. The skin was dry, coarse and rather pigmented with numerous raised waxy plaques (Figs. 2 and 6a).

Fat distribution was not abnormal except that there was very little fat at all. The arms and legs looked thin and skinny and one wondered how the latter could ever have supported the huge distended barrel-like body. The breasts were pendulous, there was no obvious glandular enlargement, and the thyroid gland was not enlarged. There was no obvious cardiac or pulmonary abnormality. The dyspnoea was considered to result from compression from below the diaphragm.

The abdomen was grossly distended by fluid and the skin was stretched as if to the point of rupture. The whole abdomen was dull on percussion and it was not possible to say whether the fluid was encysted or ascitic. She had a girth of 57 inches and the abdomen was pendulous besides being distended, so that from the front view only the knees were visible and not the thighs.

The clitoris was little if any enlarged and the external genitals were normal. Some rectocele was present and there was an old tear of the cervix. Vaginal examination did not indicate any nodularity or mass in the pelvis but only a fullness or bulging such as one finds from a large cyst or gross ascites.

It was recognized that the patient had an ovarian pathology associated with masculinization and arrangements were made to admit her to hospital the following day.

Investigations

Blood

The haemoglobin level was 87 per cent. The white blood count 6,300 per c.mm., the packed cell volume 45 per cent and the erythrocyte sedimentation rate 58 mm. per hour. On the

blood film the red cells were mainly normal but there were scattered microcytic and hypochromic cells. The glucose tolerance test was normal.

X-rays

A straight abdominal X-ray showed the whole area to be obscured by shadow without fluid levels. The appearance suggested a large cyst filling the whole abdomen. A chest X-ray showed considerable quantities of free gas present in the subphrenic region and this was causing elevation of the right diaphragm in particular. There was no evidence of secondary deposits in the lungs. The pituitary fossa was also X-rayed and was shown to be normal in outline and size.

Urinary Endocrine Products

The pregnanediol output was 3·2 mg. per day, the 17-ketosteroids 5·2 mg. per day and the 17-ketogenic steroids 18·8 mg. per day. The oestrogens were at a level of 30 international units per day and no gonadotrophins were detected at a level of 3 mouse units per day.

Operation

Laparotomy was done on 5th June, 1956, under general anaesthesia. A small incision in the midline opened through the thin abdominal wall directly into the peritoneal cavity, and it was at once apparent that there was gross ascites. Altogether 10 gallons of straw coloured fluid was sucked out and measured and thereafter the wound was enlarged to give proper access to the pelvis. The caecum and ascending colon were noted to be floating in the large volume of fluid but the small intestine remained on the posterior abdominal wall. The surface of the peritoneum was reddened and inflamed.

The uterus and right ovary appeared normal but the left ovary was enlarged to the size of a Seville orange, being quite round, white and solid-looking except for a few very bright red papilliferous projections on the outer surface. The uterus and both tubes and ovaries were removed and the abdominal wound carefully closed. The recti had been pushed away laterally and thinned out so that there was enormous redundancy of tissue. The patient was well at the end of operation and there had in fact been very little loss of blood.

Pathology

The specimen was described and reported on as follows: "The specimen consists of uterus, tubes and ovaries. The uterus is smaller than normal (65×40×25 mm.) and the histological picture is one of generalized atrophy. The cavity of the uterus is occupied by a senile type cystic endometrial polyp. The tubes were not examined histologically but their naked eye appearance is normal. The right ovary is small and histologically shows no abnormality. The left ovary is replaced by a roughly spherical tumour, 60×60×40 mm., weight 82·5 g., from which two polypoid masses have been extruded, one at the upper and one at the lower pole, through a dense, white capsule (Fig. 3). On cut section the tumour consists of rather soft, but firm, bright yellow nodular masses, interspersed with zones of haemorrhage. Histologically the tumour consists of masses of polyhedral cells, arranged in clusters, roughly resembling the outer zone of the adrenal cortex and supported by fine reticular fibrous tissue. The individual cells also closely resemble adrenal cortical cells, having a central round nucleus, and abundant clear cytoplasm (Fig. 4). In frozen sections, the cytoplasm contains a large amount of doubly refractile lipoid material. Processed sections show the cytoplasm to contain a fine interlacing fibrillary network with small nodules of brown pigment. Fuchsinophil granules (Broster and Vines, 1933) are not demonstrable. Extremely few mitotic figures are present. The histological picture indicates that this is a Masculinovoblastoma of the Ovary."

Chemical Fractionation of Tumour Tissue

We are greatly indebted to Dr. Heinz Breuer of the University Surgical Clinic, Bonn, who undertook the chemical extraction and analysis of a part of the tumour tissue. An alcoholic extract of the tissue was separated into neutral and phenolic fractions.

Neutral Fraction

Zimmerman reaction indicated 50 μg. of 17-ketosteroid in 17·8 gr. of tumour (281 μg. per cent). But no dehydroandrosterone, androsterone, aetiocholanolone, testosterone, or $\triangle^4$ androstendione were detectable by paper chromatography.

Phenolic Fraction

Oestrogens were not demonstrable.

Post-operative Progress

The patient did very well, the wound healed satisfactorily and she was discharged from hospital on 26th June, 1956.

The urinary endocrine assays were repeated post-operatively (19th June), and the reports were as follows: pregnanediol 1·3 mg. per day, 17-ketosteroids 3·0 mg. per day, 17-ketogenic steroids 9·2 mg. per day, oestrogens 10 international units per day and gonadotrophins 5 mouse units per day.

The patient's weight on 18th June, 1956, was 116 pounds (cf. 198 pounds pre-operatively).

Follow-up

20th July, 1956. She was now symptom-free and needed to shave less frequently. The scalp hair was beginning to grow again in bald areas. The abdominal skin was thick and wrinkled like an elephant's hide, but the scar was sound. Her general appearance was less masculine.

4th January, 1957. She was generally much fitter and needed to shave only twice weekly. The hair on the scalp was growing strongly and her configuration was now definitely feminine.

14th June, 1957. The general improvement was maintained, and the facial hair was falling out. The very coarse hair on the legs and body had fallen out and was replaced by very fine thin hair which was hardly noticeable.

30th November, 1957. She still had to shave off odd hairs on her chin but these were scattered and few, and the upper lip needed no attention at all. The configuration was quite feminine now and the redundant abdominal skin had largely been taken up. She was in all respects fit and well (Figs. 5 and 6b).

The patient is a highly intelligent woman and it might well be asked why she ever let herself get into such a state of abnormality. Apparently she had been seen in the early stage of masculinization but misunderstood the discussion by the doctor or doctors and thought she was destined to "turn into a man". She was so terrified of this possibility and so much in love with her husband that they both shied away from doctors and decided to let nothing interfere with the happiness they already enjoyed. The pressure of events, in more senses than one, forced them to alter their views and seek help. Now she is a happy and exceedingly grateful individual.

Summary of Case

The case is undoubtedly one of lipoid masculinizing tumour of the ovary, or masculinovoblastoma. It corresponds in almost all its features with cases previously described except for the gross ascites. There was no other or accompanying condition to account for the ascites and this has not returned since operation. It would seem therefore that a gross degree of ascites may be caused by this tumour and it is important to record this. Calmenson, Dockerty and Bianco (1947) in a review of 20,000 pelvic tumours recorded the occurrence of Meigs' syndrome in 9 cases associated with ovarian tumours and amongst these masculinovoblastoma was not included.

In this case, despite the delay in treatment, there was no shift towards malignancy and this might confirm the impression that the likelihood of malignancy is small. There are in fact only 2 recorded cases in the literature (Rottino and McGrath, 1939; Burkett and Abell, 1944).

A further feature of interest in this case lies in the low level of 17-ketosteroid excretion prior to operation. This was well within normal limits, despite the well-developed signs of masculinization. Reference was made earlier to the relationship between the symptomatology of these cases and that of the adrenogenital syndrome, and this patient showed *inter alia* some measure of hypertension. In cases of adrenogenital syndrome Jailer (1953) showed that there is a block in the biosynthesis of

hydrocortisone with the over-production of its precursor, hydroxyprogesterone. In the present case, the 17-ketosteroid and the 17-ketogenic steroid excretion levels were of such low order that further investigation on these lines did not seem profitable.

Histogenesis

One of the major features of interest in the study of these tumours centres on their aetiology. They have been regarded by various authors as hypernephromata, as tumours arising from heterotopic adrenal cortical tissue, from corpus luteum tissue or theca lutein cells, from the ovarian cortical stroma and from cells of male type surviving from the undifferentiated foetal gonad stage. It is now generally agreed that the ovarian cortical stroma is not merely a supporting connective tissue structure for the follicles and corpora lutea, but an undifferentiated mesenchymal mass from which both epithelial and non-epithelial structures may arise, and these structures may be either definitive in type or tumour tissue. The term hypernephroma, applied to the ovary, is open to as much objection as when applied to the kidney. The clear cell pattern carcinoma of the kidney is now recognized as one manifestation of a solid renal carcinoma bearing no relationship to the adrenal. It is equally possible that the lipoid tumour of the ovary stems from the parent ovarian tissue and this will be discussed later. Regarding the possibility that such tumours may arise from formed corpus luteum tissue, it is difficult to believe that a structure so evanescent, so highly differentiated and physiologically functional as the corpus luteum should be capable of tumour growth.

There has been no record in the cases described in the literature of a study of the nuclear sex chromatin distribution within these tumour cells but in the case described here the nuclear structure leaves one in no doubt that the cell is essentially feminine in genetic origin (Fig. 7), and this observation helps to rule out any possibility that the tumour arose from male cells surviving from the undifferentiated foetal gonad.

We are left therefore with the consideration of two major possibilities as to the origin of these tumours, namely that they arise from heterotopic adrenal tissue, or from ovarian stroma. In considering these possibilities it must be remembered that Willis (1948) has emphasized two important principles when considering the histogenesis of tumours in any region, but particularly in relation to the ovary. "The derivation of any tumour or class of tumour from vestigial or heterotopic tissues should not be admitted until it is certain that the normal tissues of the organ are incapable of producing such tumours; and 'embryonic rests' should not be invoked to avoid difficulties." Unfortunately embryological considerations do not allow one lightly to dismiss the evidence that these tumours could arise from heterotopic adrenal cortical tissue. The gonad, developing as it does as a genital ridge on the mesonephros, takes over, as the latter degenerates, its general attachments, and in particular its diaphragmatic ligament. This extends upwards from the mesonephros to the region of the diaphragm where it is intimately related to the developing adrenal cortex. The subsequent descent of the ovaries is liable to result in detachment of adrenal tissue, and in fact heterotopic adrenal tissue is well known to occur in the broad ligament. Opinion is divided as to whether such heterotopic tissue is included within the ovarian anlage; Meyer (1931) has demonstrated a nodule of this type within a foetal ovary and other workers are generally agreed that this may occur (Varaldo, 1904; Downes and Knox, 1924; Sternberg, 1926). In contrast Curtis (1946) regards the presence of adrenal rests in the ovary as an exceedingly rare occurrence. In an attempt to solve this aspect of the problem a series of ovaries taken during one year's routine histology was re-examined. Heterotopic adrenal tissue was found in the ovarian hilum or adjacent mesovarium in 85 cases (12·8 per cent) and it is probable that if serial sections in all cases could have been examined the percentage would be considerably higher. The amount of this tissue varied from a few isolated cells to small macroscopic nodules; for the most part they were situated adjacent to the main entrant blood vessels but a few were found near the nerve bundles. In no case was there an associated history of masculinization. A typical example is shown (Figs. 8 and 9). The

FIGS. 1 and 2
Pre-operative condition.

FIG. 3
Ovarian tumour and uterus.

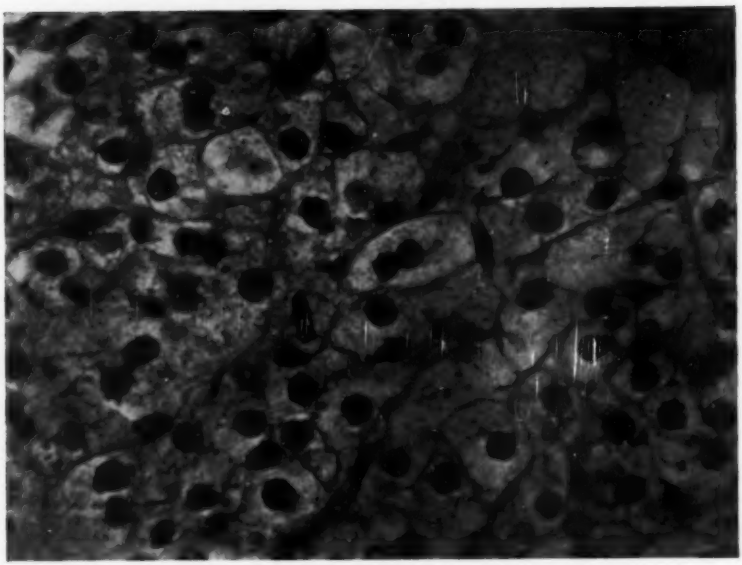


FIG. 4
Lipoid masculinizing tumour. Histology. H. & E. ×336.

D.H.L., C.G.P.

FIG. 5
Eighteen months post-operative condition.

D.H.L., C.G.P.

FIG. 6a
Pre-operative condition.

FIG. 6b
Eighteen months post-operative condition.

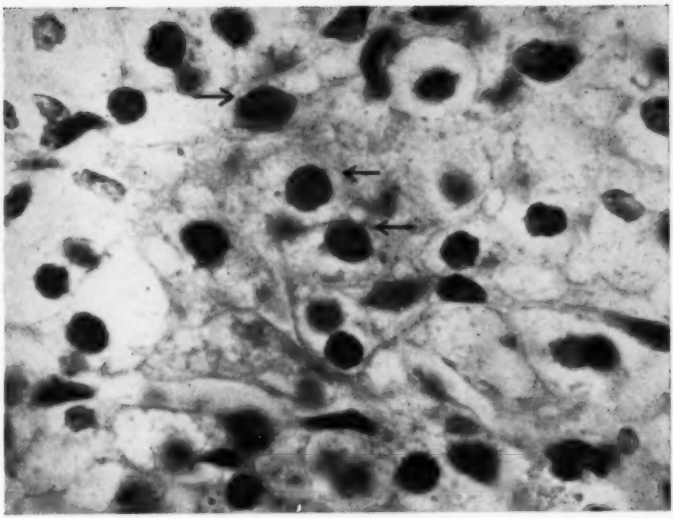


FIG. 7

Lipoid masculinizing tumour showing feminine nuclear sex chromatin. Iron Haematoxylin. ×1100.

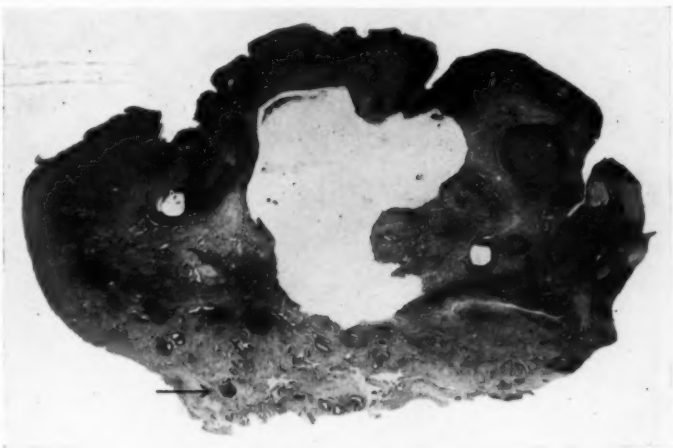


FIG. 8

Ovarian hilar adrenal rest. H. & E. ×3.

D.H.L., C.G.P.

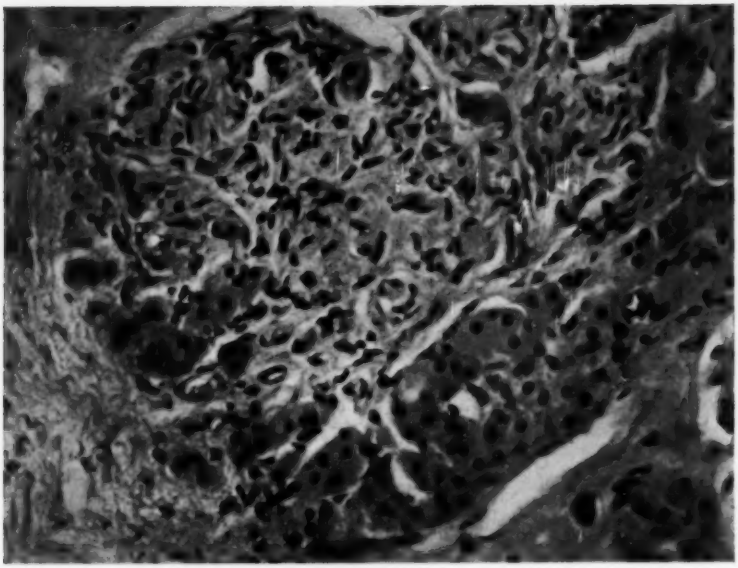


FIG. 9
Ovarian hilar adrenal rest. H. & E. ×288.

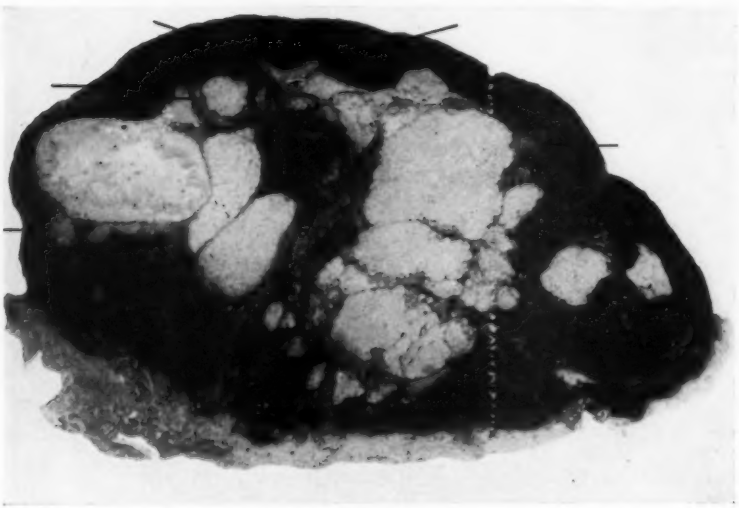


FIG. 10
Ovarian cortical hyperplasia with lipoid-type cell transformation of stromal cells. H. & E. ×3.

D.H.L., C.G.P.

FIG. 11

Lipoid-like cell transformation. Enlargement of detail of Figure 10. ×180.

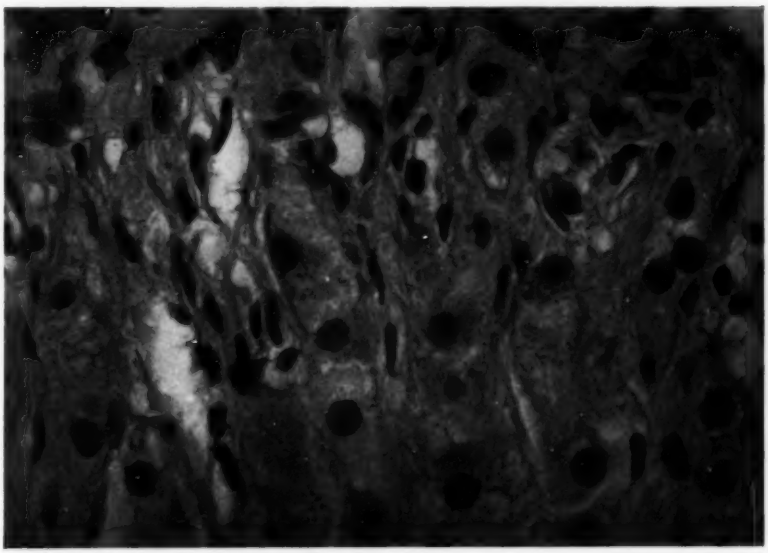


FIG. 12

Lipoid-type cell transformation. Enlargement of detail of Figure 11 showing cytoplasmic granulation. ×500.

D.H.L., C.G.P.

TABLE I

Percentage Age Distribution

	Lipoid Masculinizing Tumours		Adrenal Heterotopia 662 Cases	All Ovarian Tumours (5,353) (Selye)
	At Laparotomy	At Onset of Symptoms		
Under 20	9·4	23·3	0·0	8·1
21–30	28·1	40·0	12·8	17·8
31–40	31·3	16·7	7·4	20·6
41–50	15·6	10·7	11·6	22·8
51–60	6·2	6·7	21·9	18·9
61–70	9·4	3·3	19·7	9·1
Over 70	0·0	0·0	22·2	1·8

percentage distribution was then determined, and compared with a similar distribution for the recorded cases of lipoid masculinizing ovarian tumours, and that of a series of all ovarian tumours (Selye, 1946). The details of this comparison are set out in Table I.

It will be seen that there is a trend for lipoid masculinizing tumours to arise in the early phase of reproductive life, whereas ovarian hilar adrenal heterotopia is found most frequently in the post-menopausal era. It may well be that the higher rate of occurrence of ovarian adrenal tissue at this stage is related to that phase of anterior pituitary hyperactivity usually found in the post-menopausal era. It would be expected if lipoid masculinizing ovarian tumours arose from the heterotopic adrenal tissue that the two age incidences would to a large measure coincide, but this is not borne out in the examination of the limited material available. Iverson (1947) in his review of 95 cases showed that there is no significant difference in the age distribution of arrhenoblastoma (31·86 years mean with limits 15 and 66 years, 75 cases) and masculinovoblastoma (31·7 years mean with limits 15 and 61 years, 20 cases).

Several observations have been made to support the view that these tumours arise from ovarian tissue. Searle *et al.* (1948) described a case wherein the onset of symptoms occurred during pregnancy. In the tumour removed after delivery the usual adrenal-like tissue predominated, but this appeared to merge at the periphery into theca-type cells. The authors considered the possibility that this tumour arose from persistent elements of the corpus luteum of pregnancy; objections to this possibility have been raised by many writers, but it is possible that the theca cell elements described by the authors represented a stage in the translation from ovarian stroma to the lipoid type cell forming the main mass of the tumour.

Curtis (1946), in reporting a tumour of this type occurring in a girl of 23 years, drew attention to the variability in cellular form and illustrated his article by a photomicrograph showing a similar transition from ovarian stroma.

Iverson (1947) described a tumour occurring in a woman aged 61 years in which he compared two nodular areas, one of which showed the typical appearance of a lipoid tumour and the other the characteristics of an arrhenoblastoma. The author, after a careful review of the evidence, concluded that all functional ovarian tumours arose from undifferentiated ovarian mesenchyme; it is exceedingly difficult to believe, in his case, that the tumour could have been of the collision type, resulting from the fortuitous and simultaneous development of two tumours, both rare in incidence, and both masculinizing.

Schiller, in a discussion of a paper by Sophir (1939), in contrast came to the general conclusion that these tumours were of adrenal origin, largely because he was dissatisfied with the evidence that they could be of ovarian origin. He argued that luteoma if arising from ovarian tissue could arise either by luteinization of

ovarian tissue cells, followed by neoplasia, or by neoplasia followed by luteinization; he considered that the luteinized granulosa cell tumours were examples of the latter process and that all such tumours would be feminizing. An origin from these theca cells he regarded as improbable because these were connective tissue in type whereas the tumour cells were epithelial; an origin from granulosa cells would be betrayed in tumour tissue by the presence of either single or multiple cytoplasmic strands between adjacent cells. The well demarcated cell boundaries of the lipoid masculinizing tumours did not, in his view, permit of an origin from granulosa cells with subsequent luteinization. His views are in conflict with those of Zwemer, Wotton and Norkus (1938) who showed that adrenal cortical cells, pre-eminently ones with well demarcated cell boundaries, are regenerated from the mesenchymal fibrous tissue capsule of the adrenal.

Evidence, apart from tumour formation, that luteinized ovarian cells may be associated with masculinization, is suggested by Stein and Leventhal (1935) and Stein and Cohen (1939) who described, in addition to multiple follicular cysts, theca luteinization related to amenorrhoea and masculinization. Fraenkel (1943) also described a syndrome of masculinization associated with diffuse hyperplasia of theca cells. Such cases are apparently rare, but the author has seen one such case occurring in a woman aet. 71 years who complained of symptoms of masculinization. At operation one ovary was replaced by a unilocular pseudomucinous cyst; the other ovary was the site of gross cortical stromal hyperplasia and at several areas along the inner border of the cortical stroma, a transition from ovarian stromal cells to large lipoid-containing polyhedral cells, was demonstrable (Figs. 10, 11 and 12).

On the experimental side evidence is not lacking to indicate that pathways of metabolism exist to allow of androgen production from steroid compounds essentially feminizing. Rottino and McGrath (1939) and Iverson (1947) have drawn attention to the androgenic effects produced in spayed female guinea-pigs by the injection of progesterone, and Jailer (1953) has shown that hydroxyprogesterone is the precursor of androgenic substances produced by the adrenal in cases of adreno-genital syndrome.

In conclusion, it may be said that the case for masculinizing ovarian lipoid tumours arising from aberrant adrenal tissue, rests upon a close histological similarity and the fact that ectopic adrenal tissue can be found in and near the ovarian hilum; but when such tissue has been demonstrated, masculinization has not been recorded. The age distribution of these tumours, so far as can be determined, is the same as that for arrhenoblastomata, whereas adrenal rest tissue is more evident in a much later age group. On the other hand, in some of the tumours, a transition between the large polyhedral lipoid cells and the spindle cells of the ovarian stroma has been noted. A transition has been seen also in tumour-free ovarian stroma, this transition being associated with masculinization. Luteinization of ovarian tissue and ovarian tumours is normally associated with hormonal changes essentially feminizing in character, but undoubtedly chemical pathways exist whereby steroids allied to feminizing activity may be converted to those having androgenic effects. It seems probable therefore that the ultimate solution of this problem will be a chemical one. At present the evidence suggests that these tumours most likely arise from the highly potentiated ovarian cortical stroma.

We wish to acknowledge our indebtedness to Mr. Larway, Photographic Department, United Sheffield Hospitals, and to Mr. H. Dyson, F.I.M.L.T., for technical assistance.

References

Barzilai, G. (1943): *Atlas of Ovarian Tumors*. Grune and Stratton, New York.

Broster, L. R., and Vines, H. W. C. (1933): *The Adrenal Cortex: A Surgical and Pathological Study*. Lewis, London.

Burkett, J. A., and Abell, I. (1944): *Surg. Gynec. Obstet.*, **79**, 651.

Calmenson, M., Dockerty, M. B., and Bianco, J. J. (1947): *Surg. Gynec. Obstet.*, **84**, 181.

Curtis, A. H. (1946): *Amer. J. Obstet. Gynec.*, **52**, 115.

Downes, W. A., and Knox, L. C. (1924): *J. Amer. med. Ass.*, **82**, 1315.

Fraenkel, L. (1943): *J. clin. Endocrin.*, **3**, 557.

Iverson, L. (1947): *Surg. Gynec. Obstet.*, **84**, 213.

Jailer, J. W. (1953): *Bull. N.Y. Acad. Med.*, **29**, 337.

Meyer, R. (1931): *Arch. Gynäk.*, **145**, 2.

Rottino, A., and McGrath, J. F. (1939): *Arch. intern. Med.*, **63**, 686.
Searle, W. N., Haines, M., and Baker, J. K. (1948): *J. Obstet. Gynaec. Brit. Emp.*, **55**, 135.
Selye, H. (1946): *Encyclopedia of Endocrinology, Section IV. Volume VII. Ovarian Tumors.* Richardson, Bond and Wright, Montreal.
Sophir, O. (1939): *Amer. J. Obstet. Gynec.*, **37**, 1008.
Stein, I. F., and Cohen, M. R. (1939): *Amer. J. Obstet. Gynec.*, **38**, 465.
Stein, I. F., and Leventhal, M. L. (1935): *Amer. J. Obstet. Gynec.*, **29**, 181.
Sternberg, C. (1926): *in* Halban and Seitz: *Biologie und Pathologie des Weibes.* Vol. II, p. 675. Urban and Schwarzenberg, Berlin.
Varaldo, F. (1904): *Arch. Ostet. Ginec.*, **11**, 725.
Willis, R. A. (1948): *Pathology of Tumours.* Butterworth, London. p. 481.
Zwemer, R. L., Wootton, R. M., and Norkus, M. G. (1938): *Anat. Rec.*, **72**, 249.

THE HISTOGENESIS OF OVARIAN TUMOURS

BY

R. E. REWELL,* M.D., M.R.C.P.

From the Government Hospital for Women and Children, Madras, 8, India

SECTION I

MATERIALS USED AND SOME GENERAL CONCLUSIONS THEREFROM

As compared with other organs the ovary is not uncommonly the site of a tumour, especially if simple cysts of the follicle produced by dilatation at various stages in its life cycle are considered. Adenomas and adenocarcinomas are moderately frequent, but what are usually known as the "rare tumours of the ovary" are truly rare, some very rare indeed, and it is this which makes them available as a rule only to specialists, despite their theoretical interest. Every student knows of the masculinizing effects of ovarian arrhenoblastoma and how they can be differentiated from those due to suprarenal cortical tumours, but so rare is the arrhenoblastoma that no example is found in the present series which includes all the ovarian tumours examined at two large gynaecological centres on opposite sides of the world during several years, although sections of a single case were available for study.

The two institutions concerned are the Women's Hospital, Liverpool, England and the Government Hospital for Women and Children, Madras, India, which now houses the Institute of Obstetrics and Gynaecology, the main postgraduate teaching centre in this speciality for all India. At the former centre, blocks and sections of all specimens have been kept since the beginning of 1950 and were available for me to examine until the end of 1955. At the latter centre I have reviewed a similar series from mid-1953, when correct filing methods were adopted, until mid-1957, the time of writing. Rather more in-patients are treated in Madras each year than in Liverpool. I have with me in Madras for analysis figures from Liverpool for only the four years 1950–1953 inclusive, but this covers the same length of time as the series from here. Like all people who work in a limited field, doubtful and interesting tumours are sent to me from elsewhere from time to time, so that I have seen a greater number of the "rare" tumours than would appear from the Table. The total number of all tumours examined must be in the region of 500, perhaps a little more. Follicle, luteal and theca-lutein cysts are not included in this figure, nor the common form of simple cyst with a thin, fibrous wall in which the lining epithelium is so compressed as to be unrecognizable. The study suffers from being retrospective. No more blocks can be taken from the original material and a very limited range of staining techniques can be applied.

TABLE I

Diagnoses of Ovarian Tumours in Liverpool and in Madras for a Four-Year Period

Diagnosis	Liverpool	Madras
Fibroma	23	4
Pseudomucinous cystadenoma	63	33
Serous cystadenoma	37	9
Adenocarcinoma	34	37
Secondary carcinoma	13	8
Teratoma	30	14
Brenner	3	2
Dysgerminoma	0	3
Granulosa-cell	5	5
Sarcoma	0	1
Angioma	0	2
	209	118

* Professor of Pathology, University of Madras, under the Colombo Plan. Permanent address: The Women's Hospital, Liverpool 8, England.

Table I shows the types of tumour found at the two centres. The criteria for the diagnoses will be discussed more fully below in Section III of this paper, but for the present such discussion is not necessary. The lower total in Madras as compared with Liverpool is difficult to explain. It may be that in England, where the family doctor is a well-established institution, better diagnosis at the periphery may send more patients to the correct special hospital rather than to a general one. However, in Madras cases diagnosed as ovarian disease at a general hospital are normally transferred to a special one. The greater frequency of fibroma in Liverpool is probably explained by the greater number of ovaries removed there, most of the tumours so described being small and chance findings. Far fewer abdominal hysterectomies are performed in India as patients expect gynaecological procedures to be conducted *per vaginam* and the abdominal route is chosen only when essential. These tumours were submitted to frozen section as a routine to exclude the presence of fat and hence the diagnosis of thecoma. Serous cystadenoma appears to be less common in Madras. The numbers of the rarer tumours are too small for valid comparison, but it is probable that granulosa-cell tumour and possible that dysgerminoma are more frequent in Madras. The very close correspondence in relative proportions to the total of pseudomucinous cystadenomas, teratomas and secondary carcinomas in the two centres is striking. With three exceptions the secondary carcinomas in India had an endometrial origin. Endometrial cancer is much less common here than in England, but appears to arrive at hospital with secondary spread to the ovaries in a high proportion of cases; in fact the patients often present with the ovarian tumour causing the main symptoms. Of the other three secondary tumours in Madras one was from an epidermoid carcinoma of the cervix, one was a typical Krukenberg tumour with an evident gastric primary and the other was thought to be of intestinal origin, but the patient discharged herself before search for it could be made.

The greater frequency of primary adenocarcinoma in Madras is striking also and appears too great to be due to chance. No explanation is offered. In South India the condition shows no unexpected clinical or morbid anatomical features.

In view of the hard things that are said by some of the present-day experimental "anatomists" it seems as well to reiterate that the routine histology at any large gynaecological centre involves the examination of thousands of human ovaries. The range of techniques employed is limited and it is often objected that such organs must be abnormal. However, many are certainly normal, e.g., those removed for ectopic gestations. Such ovaries reveal the important fact that the structure of many removed for such conditions as endometrial hyperplasia is certainly within normal limits. Conversely gross structural abnormality is sometimes perfectly compatible with normal genital function, e.g., an ovarian tumour discovered accidentally during Caesarean section which proved to be a thecoma (case of Mr. Harold Francis—not included in Table I).

Section II

Observations on the Normal Ovary

It appears rather late in the day to add anything to this subject by ordinary methods and this section must consist largely of well-known facts, but chosen to illustrate the main thesis. The human ovary, then, is covered by a layer of the so-called "germinal" epithelium, under which lies a fibrous capsule. It is not often realized, however, that this fibrous capsule is absent in infancy and seems to develop only round about the time of puberty. The pubertal ovary is a rare specimen, but I have seen a few from young girls in which a definite history was obtained that only one or two menstrual periods had occurred, while in one or two others previous menstruation was denied emphatically, but a recent corpus luteum was present. The history is unfortunately often defective for specimens obtained at this age, e.g., from girls killed in accidents.

The normal infantile ovary consists, of course, of close-packed ova, each surrounded by a thin rim of epithelial cells which later develops into the follicle lining, these immature follicles being

separated by a minimum of stroma. At the time of puberty the stroma increases in amount, some of the follicles develop fully, while others atrophy. Many of these latter appear to be caught up in the developing fibrous capsule of the organ, as shown in Figure 1. This is from a girl aged 14 who claimed to have had only two periods separated by an interval of four weeks. These observations are matters of fact and it should be noted that they are independent of controversies as to whether or not follicles arise from the superficial epithelium of the ovary and as to whether or not new follicles arise in the adult ovary.

As for the normal ovarian stroma it is often described as ordinary fibrous tissue, but in fact this must make up only a small proportion of the whole. The fibrous capsule has been mentioned already and usually forms a definite layer distinct from the underlying ovarian stroma. This is especially marked when the capsule hypertrophies and forms the stroma of such tumours as adeno-fibroma, the early stages of which can occasionally be found on the surface of what appeared grossly to be a normal ovary. Sometimes multiple sites of origin for it are evident and sometimes atretic follicles can be caught up in the hypertrophying fibrous tissue. The fact that what appears to be normal fibrous tissue can multiply greatly in the ovary under certain stimuli, e.g., in the Krukenberg tumour, proves nothing as to its usual proportions in the normal organ.

As is well known the usual ovarian stromal cells are larger than those of the capsule, with larger, plumper nuclei. They commonly lie with their long axes side by side in groups and have a characteristic wavy form, the pattern being easily recognized in sections of doubtful origin. They cannot easily be distinguished from the cells lying next to a follicle, in fact the usual description is that the outermost layer of the follicle, the theca externa, blends imperceptibly with the ovarian stroma. This may be so, but there is often no obvious distinction between cells adjacent to a follicle and those lying far away from one, while in such tumours as the fibroma and thecoma the distinction is possible only using histochemical methods, of which more presently.

The identity in appearance of cells from the two sites is admitted universally in the mature corpus luteum where the supporting "paralutein" cells are described as appearing like typical fibrous tissue, but as capable of undergoing luteinization if the process is prolonged, as in pregnancy. In such a prolonged state of luteinization many scattered cells throughout the ovary undergo this change. It is usually held that these cells are associated with follicles which have ceased to be active, but it is by no means obvious that this is so for every such group. Especially when the follicles become cystic the "merging" of the thecal cells with the surrounding stroma that is usually described becomes a merging of the theca of adjacent follicles, while many ovaries without many dilated follicles show a stroma which is indistinguishable from theca. An interesting instance occurs in the rare and unexplained cases of luteinized follicle cysts in the neonatal ovary. Here the ovarian stroma becomes greatly increased in amount and the cells become plump and resemble theca closely, even in areas where no luteinization is evident.

Histochemical methods which have been used to distinguish between thecal cells and ovarian stroma have been touched on already. In practice the only one which has stood the test of time is that of staining for fat by a variety of methods in frozen sections. Examination for birefringent crystals of unstained frozen sections under polarized light, although strictly perhaps not a histochemical method, can be included with fat-staining. Granulosa cells also contain fat and the test has been used in the classification of tumours on the borderline of this class, those which show no fat being excluded from it.

It seems clear, however, that like any other single criterion, the test must be used with caution. Little experience is necessary to show that some tumours which are typical of the granulosa variety contain much less fat than others, nor do all the cells stain equally well in the same area. In fact there is no histological criterion by which one can judge whether or not any individual cell, either in different tumours or in the same tumour, will take up fat stains. This is most obvious for the granulosa cell, but the same applies to the thecal cell, both as

regards stainable fat and birefringent crystals. In fact, although in organs "structure depends upon function", at the level of the individual cell and using these methods there is no strict dependence of morphological upon physiological differentiation.

The difficulty is increased by the present impossibility of measuring the functional activity of follicle cells. Even for a granulosa-cell tumour in a pre-pubertal or post-menopausal subject, hormone levels in blood and urine can bear only a very rough relationship to their rate of production. The enormous individual variations in response make, moreover, such changes as those in the histology of tubal mucosa or endometrium and in the cytology and histochemistry of the vagina, of purely qualitative significance and no attempt can be made to draw quantitative conclusions from them.

Histochemistry, therefore, must be used with discretion in the classification of ovarian cells, both in the normal ovary and in tumours. This has been brought home to me lately in the stroma of pseudomucinous cystadenomas. In a previous communication (Rewell, 1957), when discussing the relationship between these and Brenner tumours I pointed out that little seemed to be known about the stroma of pseudomucinous cystadenomas. Since that time I have studied the stroma in many old sections and have found a wide variety of types, from typical fibrous tissue to much plumper cells with larger nuclei indistinguishable from theca by ordinary methods. Since writing the previous paper 12 pseudomucinous cystadenomas have been received in this Department and several blocks from each have been cut on the freezing microtome and fat stains applied. In one example intracellular fat granules were demonstrated in about one stromal cell in five and these cells were of a type intermediate between the two extremes mentioned. I would not wish to force these into the definition of theca by virtue solely of their histochemical reactions, nor to draw any inference from their behaviour as to the origin of pseudomucinous cystadenomas. But more of this below. The stroma immediately beneath the mucin-bearing mucosa may vary greatly. Cells of the Brenner type are well known to occur there even in quite large individual cysts. Figures 2 and 3 show cells from below the mucosa in different pseudomucinous cystadenomas.

It must be concluded that the stromal cells of the normal adult ovary are much more like the thecal cells of the follicle than is generally admitted. It may be that thecal cells spread out from follicles, or that the stroma of the adult is in a large part derived from the rim of cells round each ovum of the infant, or yet again that the cells of the stroma happen to respond in an unusual way to hormonal activity owing to their proximity to the site of production. In any case they are not simple fibrous cells. Their role in the histogenesis of ovarian tumours must now be discussed.

Section III

The Structure of Some Ovarian Tumours

(a) *Granulosa-cell Tumours*

There is no doubt that the well-differentiated tumour of this class reproduces the characteristics of the lining of the mature ovarian follicle especially of the innermost lining which gives the tumour its name. However, there is no less doubt that the tumour is by no means composed of mature granulosa cells alone. Even in the best-differentiated examples thecal cells abound. Granulosa-cell tumours are fairly rare, well-differentiated examples are usually the ones illustrated in books and articles and so it is not generally realized that the usual form of the tumour is the poorly-differentiated or "diffuse" type in which irregular masses of granulosa cells are found without any follicular arrangement. Sometimes these tumours infiltrate widely. They always contain large and irregular areas of thecal cells and in some it is not possible to decide without many sections which is in the majority. This inextricable mingling of the two tissues has been emphasized by Willis (1948). To my mind such growths are best described as "tumours of the ovarian follicle" as they contain both elements. Clinically, if they produce hormones at all these are always oestrogens, however much the thecal element may predominate, until one gets to the tumour consisting virtually of thecal cells alone. It may be possible to show

mixed function of tumours by means of vaginal smears. Thus from a recent case of post-menopausal vaginal bleeding a smear taken before operation showed with Papanicolau's stain both acidophil epithelial cells suggestive of oestrogenic activity and clumping and curling of basophil cells suggestive of a progestational effect. The patient proved to have a well-differentiated "granulosa-cell" tumour with large areas of theca. In the standard method of classification all these tumours are described as "granulosa-cell" except those consisting almost entirely of theca. This is of clinical convenience and has been used in constructing Table I, but it expresses incompletely the facts of histology (Figs. 4 and 5).

Harvey, Dawson and Innes (1940) in a well-known discussion of this tumour implied that the cytology was uniform in all, although Willis (1948) held that it varied considerably and that there was no clear distinction between these cells and those of some other tumours, notably the Brenner type. Although I must agree that the two tumours differ cytologically in most examples (Rewell, 1957), recent review of my old material with the addition of some new examples has shown me that this is by no means always the case. Figure 6 shows a good instance of this, the mucin-bearing acini of a typical Brenner tumour being obvious and indeed this example was found in what appeared grossly to be the usual type of pseudomucinous cyst-adenoma. The epithelial cells are arranged in nests, but those not bearing mucin are strikingly like the accepted pattern of the granulosa cell. Indeed there is no other cell of ovarian origin whose name can be applied to them. This is not the only specimen in the present series which shows such overlapping and this fits in with the cytological and histochemical evidence already produced by Teoh (1953) and myself (1957) of the common origin of granulosa-cell and Brenner tumours.

This is not, however, all that can be learned from Figure 6. In fact it shows two more points of importance. The first is the plump, thecal type of cells which constitute its stroma and the second is the way in which the epithelial cells of the nests blend imperceptibly with them. This occurred throughout the tumour and many cells were found which it was impossible to assign to one group or the other. Similar merging of thecal and granulosa cells is frequently evident in the follicular tumours discussed above and this brings us back to the merging of theca and ovarian stroma discussed in Part II of this paper. The identity of origin of ovarian stroma, granulosa and theca is thus supported by a study of a relatively large and varied series of tumours such as the present.

(b) *Brenner Tumours*

In the previous section these tumours have been dealt with only in so far as they impinge on "granulosa-cell" and "thecal-cell" tumours, but this is not the whole story. The typical Brenner epithelial cell nest in its bed of fibrous tissue is such a characteristic appearance that it is tempting to regard it as a tumour species. However, the facts are probably best interpreted by regarding the "Brenner pattern" as a non-specific one which may be produced by several different processes, a view advanced by Greene (1950) in a careful study. Once more the tumour is rare so that, as in the case of the granulosa-cell tumour, the wide range of variation between examples is not generally realized. The stroma is variable, though usually of the same general type throughout one specimen, sometimes of typical dense fibrous tissue, sometimes much more cellular and indistinguishable from theca. The histochemistry of this point was reported upon by Teoh in the paper already quoted.

As has been implied already the epithelial cell nests vary widely in their cytology as between different tumours, although usually fairly uniform in any one tumour. It must, however, be admitted that these differences are hard to distinguish from the effect of inadequate fixation and poor staining, but too much may be attributed to such artefacts. Much also must be allowed for the mechanical deformation of cells pushed about in nests of varying shape and size, the "nest" being usually rod-shaped, the accepted illustration being of a section perpendicular to the long axis of this structure. In the pattern usually illustrated individual cells appear almost wedge-shaped, the long axis of each being vertical to that of the rod of cells. In some tumours, however, they are polyhedral

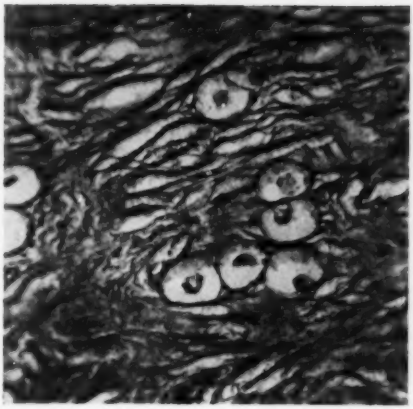


FIG. 1

Adolescent Ovary. Atretic follicles in the developing capsule. ×200.

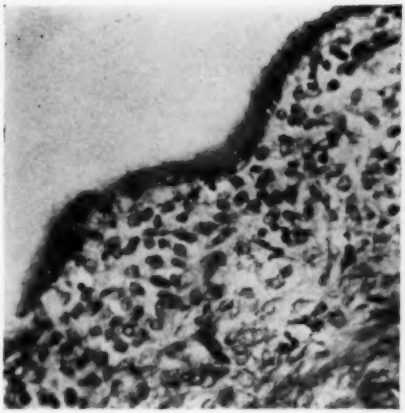


FIG. 2

Pseudomucinous Cystadenoma. Columnar mucosa overlying cellular stroma indistinguishable from granulosa. ×320.

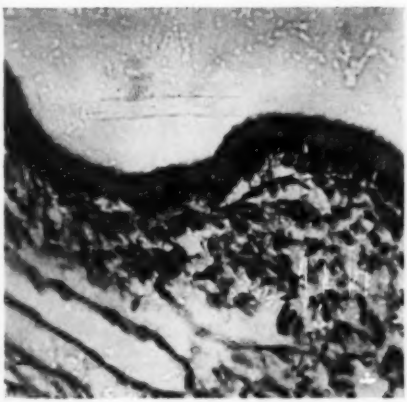


FIG. 3

Pseudomucinous Cystadenoma. Another type of cellular stroma, resembling theca. ×320.

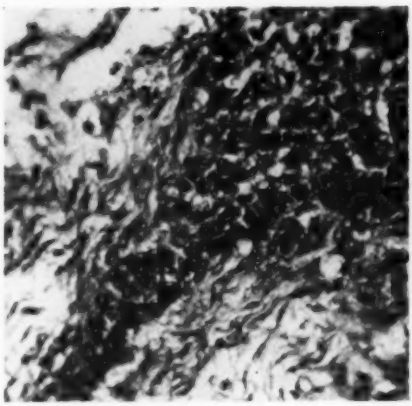


FIG. 4

Tumour of the Ovarian Follicle ("Granulosa-cell"). Juxtaposition of granulosa and thecal cells. ×320.

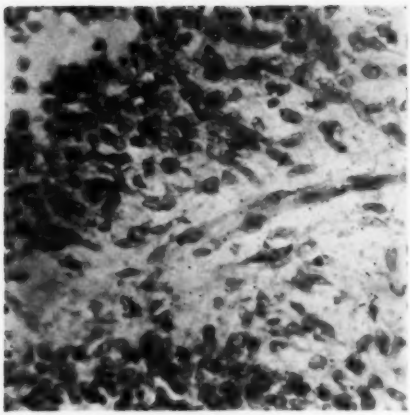


FIG. 5

Tumour of the Ovarian Follicle ("Granulosa-cell"). Mingling and merging of granulosa and thecal cells. ×320.

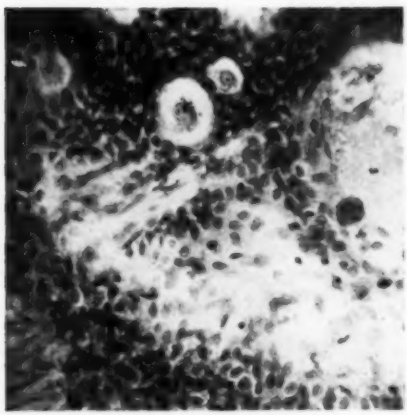


FIG. 6

Tumour of cells indistinguishable from granulosa, but producing mucin-bearing acini. They also merge with the cellular stroma which is of thecal form. Classified as a Brenner tumour when first seen. ×320.

R.E.R.

with a pale-staining cytoplasm and small nucleus. Yet again they may be smaller with large nuclei and then merge imperceptibly into the granulosa cell, as pointed out by Willis. The identity of origin of Brenner and granulosa cells from stroma has been shown above (Fig. 4). In one respect this confirms the findings of Greene that Brenner cells arise from stroma. He has demonstrated also the origin of Brenner cells from follicles, but does not point out that granulosa and Brenner cells merge into each other and cannot be distinguished in some cases.

The Brenner appearance can be produced from cells of undoubted follicular origin in another way, i.e., by the catching up of a number of atretic follicles in the developing ovarian capsule, as seen in Figure 1, or in a fibro-adenoma as mentioned above. When the cells of the atretic follicles are preserved an appearance is produced which it is hard to distinguish at first glance from the type of Brenner tumour in which the epithelial cells are larger than the average. I am not suggesting that this is an appearance which is often mistaken for a true tumour, but it does show how "non-specific" the classical Brenner pattern can be. The "malignant Brenner" tumour reported by Sirsat (1956) shows that extreme pleomorphism may be found even with a single tumour.

In one case of the present series minute, bilateral Brenner tumours were found by chance embedded deep in each ovary and with a definitely fibrous stroma. These would appear to be examples of tumours arising from the rete ovarii as demonstrated by Greene. The finding of such unusual tumours in such an unusual site in the ovary again confirms his demonstration of the diverse origins of Brenner tumours.

Oestrogenic function on the part of Brenner tumours has been noted repeatedly and recently Scully (1957) has described two, one producing an oestrogenic picture and the other masculinization. No illustrations are given and the description of the epithelial elements assumes that the standard pattern is always found, but the stroma in both examples is stated to be cellular and to resemble ovarian stroma or theca. Hormonal activity would be expected to be confined to Brenner tumours of stromal-follicular origin. Moreover, these would be expected to show plumper stromal cells than the fibrous tissue constituting the stroma of those of different origin. However, another overlap that occurs in the group is that stroma that appears at first sight to be true fibrous tissue may show thecal relationships on closer study. especially near the cell nests, as was demonstrated by Teoh. Further we must not yet forget that function and structure may not develop at equal rates. Thus the tumour shown in Figure 4 had no obvious functional activity whatsoever.

The possible origin of Brenner tumours from the surface "germinal" epithelium of the ovary and from Walthard nests has been discussed in the papers already quoted and need not be discussed again now. Suffice it to say that an origin from surface epithelium is likely, but not one from Walthard nests.

The relationship between Brenner tumours and pseudomucinous cystadenomas has been mentioned above, while Figures 2 and 3 emphasize the relationship between pseudomucinous cystadenomas and follicles. This is, of course, no new suggestion, nor need it be postulated that all these tumours arise by metaplasia within follicles. The great size of many renders complete examination impossible and it is only in small ones found by chance that such an origin may be obvious. Thus an ovary seen recently showed numerous follicle cysts, some showing pseudomucinous metaplasia and others not. If, however, Brenner tumours also may arise from stroma-follicle cells the old argument as to whether or not pseudomucinous cystadenomas arise always from Brenner tumours is seen from a new angle. The cells of Brenner nests may, of course, contain mucin even when acini are not formed. Indeed mucin secretion is a specialization which may arise in follicle cells whether they are in a developed follicle or lying deep in a Brenner nest away from a free surface and with no other mucin-bearing cells adjacent. There is no reason why some tumorous cells of follicular origin should not proceed directly to mucin formation while others arrive there via a stage of Brenner type. Thus all possible stages of the two lines of development could be seen together, i.e., in such mixed Brenner-pseudomucinous tumours the characteristic cells of both types have a common

origin, while the Brenner may pass into the pseudomucinous cell. In my previous paper already quoted I discussed how the purely mechanical appearance of secretion within the cells of a Brenner tumour nest might determine their arrangement into acini, indeed the mucin-bearing acinus itself may well be another non-specific appearance produced from a variety of cells of diverse origin by the one change of the introduction of mucin into the cell. It is not essential to assume that a mucin-containing cell is necessarily derived from a mucin-bearing stem.

Section IV

General Discussion

Perhaps the most striking point which emerged from review of this series of ovarian tumours is the manner in which several classes previously thought of as distinct were found to shade into each other. The standard types as described and illustrated in textbooks exist, of course, but they are by no means the only ones seen, nor are they necessarily the most common. Thus it is often difficult to place an individual tumour in an appropriate class, even when a number of sections are examined. Table I has been compiled from the diagnoses made as each tumour presented itself, i.e., as an individual urgent problem demanding solution as a guide to treating an individual patient. Few diagnoses have been revised on review of the sections, the original diagnosis in borderline cases usually appearing in retrospect as the most reasonable in view of all the circumstances. In some cases, of course, the diagnosis is of little importance in treatment, e.g., for a small pseudomucinous cystadenoma with Brenner areas it makes little practical difference which class it is put into. On the other hand prognosis and suggestions as to treatment may be implied in the histological diagnosis, e.g., of a poorly-differentiated and widely-infiltrating granulosa-cell tumour. In many cases discussion of all the circumstances with the clinician is the only way in which to discharge the responsibility placed on the histopathologist. It should be noted that most of the granulosa-cell tumours in the present series were poorly-differentiated and that some did indeed infiltrate widely.

The "non-specific" nature of some histological appearances, e.g., that of the Brenner tumour, must also be borne in mind when giving labels to individual specimens. The physical laws leading to the adoption of a particular shape by a particular cell under particular circumstances have been discussed in great detail for some aspects of normal life, e.g., by Thompson (1942), but they are often forgotten when dealing with morbid histology. It is indeed usually assumed that the final appearance adopted by a cell is the result of its internal constitution as laid down by the stem from which it derives. This is obviously true in one sense, but the influence of the surroundings has to be considered also. These factors can indeed be arranged in the different ranks of "causes" as laid down by Aristotle. The relative part played by ontogeny, phylogeny and environment in the formation of normal organs has been discussed by De Beer (1940). The labelling of ovarian tumours has a use and purpose provided that the foregoing considerations are borne in mind and it is realized that many of the labels applied are as artificial as those given to the continually-developing immature erythrocyte.

The teratomas in the present series require some discussion. Under this heading are included all types from the simple dermoid cyst in which only skin and its appendages were found to a single, highly-malignant tumour containing many types of tissue which killed rapidly a girl of 16 in Liverpool. The fundamentals of the development of these tumours have surely been elucidated by Nicholson (1950), but the theory of origin of many ovarian tumours by "one-sided" development of teratomas is still regarded as rational by many surgeons, surprising though this may sound to a pathologist. Complete replacement of the tumour by one tissue can take place. In the present series two fell into the rare group of *strumae ovarii*. In one an island of thyroid tissue was found with several other well-developed tissues in the wall of a dermoid cyst. The other was composed of a number of loculi, the largest about 7 cm. across and all filled with amber-coloured jelly. Nothing except perfectly-differentiated thyroid tissue was found in the sections. No symptoms or signs referable to

thyroid dysfunction were observed either before or after operation.

Despite all this, if ovarian tumours can be divided into groups derived from different cells diverging at an early stage, the series giving rise to the stroma-follicle range of tumours on the one hand and to the teratoma range on the other must differ profoundly from an early stage. The stroma-follicle range give rise to a limited number of rather specialized cell-types, while the teratomas produce many types. These differ widely from each other, influence each other's development (Nicholson), must diverge at an early stage and if functional never function in the same way as the cells of the stroma-follicle series. The fact that both series may produce mucin-bearing mucosa merely shows the intermediate position of this tissue and its "non-specific" nature capable of being produced from different cells under different conditions. The teratomas on the one hand and the stroma-follicle group of tumours on the other thus form very distinct groups and it is unlikely that one could turn into the other.

The dysgerminomas observed in the present series presented no special features. All conformed to the accepted type and were of uniform structure. None occurred in pseudo-hermaphrodites, although one (in Liverpool) was found incidentally in a recently-married woman of 29 who presented with a rigid hymen and she had a uterus which was described as "infantile". This tumour was highly malignant and killed the patient in a few months, sections of the recurrence being sent to me. One of the Indian examples killed the patient quickly also, a girl aged 14. The others have not been followed up.

Sections of a single arrhenoblastoma occurring some time ago are preserved in Madras. Sections from a small ovarian tumour in an English girl aged 16 were sent to me from a colleague's private practice and are not included in the series. This patient had masculinization which appeared to be cured by removal of the tumour. Unfortunately, fixation was poor, but the tumour appeared to be quite unlike an arrhenoblastoma, showing rosettes of cells, more like granulosa. The sections are too bad for reproduction. These cases are quoted to emphasize the rarity of masculinizing tumours of the ovary and the lack of correlation that may be found between structure and function.

Little can be added about adenocarcinoma of the ovary. All those examined conformed to the accepted pattern and all had proceeded to complete destruction of the normal ovary. All carried an exceedingly bad prognosis where follow-up was possible. It cannot be emphasized too strongly to surgeons that this is invariably the case for this tumour and that the presence or absence of a capsule makes no difference, nor does the histological grade of the tumour. The secondary tumours form a class by themselves and have little bearing on the main thesis of this paper. Little need be said either about the serous papillary tumours, whether encapsulated or sprouting on the surface of the ovary, except to say that many have a poor prognosis, a number of the English cases coming back within a year with frank carcinomatosis. In India, of course, any sort of follow-up is virtually impossible. It may be that numerous blocks would find malignancy from the start, but this is not really practicable as there is no guide as to how many would need to be taken. My own practice is to take no more than five, but to give a guarded prognosis in all tumours with a serous papillary structure.

We have, therefore, several classes of ovarian tumours which, in accordance with accepted theories, we can regard as arising from cells which branch off from each other at an early stage of differentiation. Dysgerminomas form one such line and arrhenoblastomas probably another. Teratomas certainly form a line by themselves. The biggest class, however, arise from the direct line of stroma-follicle cells. These cells are probably able to develop each from the other so the tumours that arise from them do so at a late stage of their development. There is no need to regard say the granulosa-cell or Brenner tumour as derived each from a separate line of cells diverging at a very early stage. All this group, including some pseudomucinous cystadenomas, are tumours of quite or almost adult cells, comparable to say carcinoma of the stomach or breast.

Finally the present study lends support to the theory that new follicles may arise in the adult ovary, since stromal and follicle cells appear to

change one into the other. The final stage in the differentiation of a follicle, i.e., the formation of an ovum, has not been observed.

Section V

Summary and Conclusions

A series of ovarian tumours, about 400 in all, coming largely from one centre in England and one in India is presented. Adenocarcinoma appears to be relatively more common in India than in England. Ordinary histological methods are used and some histochemical, but the limitations of the latter type of method are discussed.

The boundaries between many of the accepted types are much less clear than is usually realized, e.g., the granulosa-cell and thecal-cell tumours form a continuous series, nor can some Brenner tumours be divided from them sharply, while these again merge into some types of pseudo-mucinous cystadenoma. These tumours form a group by themselves, what may be termed the "stroma-follicle" group and they are best regarded as derived from the common stem of theca and follicle cells in the normal adult ovary at quite a late stage in their differentiation. Among these tumours structural differentiation by no means runs parallel with functional differentiation and *vice versa*. The series confirms previous observations that the Brenner appearance, and possibly that of the pseudo-mucinous cystadenoma, is non-specific and may be produced by different modes of development, nor are these in themselves of a uniform pattern. The terms "granulosa-cell", "thecal-cell" and "Brenner" applied to tumours are of clinical convenience only. These terms must not be thought of as excluding a common origin for the group, while many individual tumours fall into areas of overlap between them even when used in a purely descriptive sense.

Teratomas are probably derived from a distinct stem of primitive cells, as also are dysgerminomas and probably arrhenoblastomas.

Routine study of ovaries removed at operation confirms modern theories of the close relationship of stromal and follicle cells and tends to support the possibility of the origin of new follicles in the adult ovary.

Acknowledgments

I have to thank my clinical colleagues in Liverpool and Madras for sending me the material for this paper. The illustrations were made by our photo-artist in Madras, Shri R. Kumaradevan, D.F.A.

References

De Beer, G. R. (1940): *Embryos and ancestors*. Oxford University Press, London.
Greene, R. R. (1950): *Amer. J. Obstet. Gynec.*, **64**, 878.
Harvey, W. F., Dawson, E. K., and Innes, J. R. M. (1939): *Edinb. med. J.*, **46**, 256.
Nicholson, G. W. de P. (1950): *Studies in tumour formation*. Butterworth, London.
Rewell, R. E. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 85.
Scully, R. E. (1957): *Amer. J. Path.*, **33**, 584.
Sirsat, M. V. (1956): *J. Obstet. Gynaec. India*, **6**, 1.
Teoh, T. B. (1953): *J. Path. Bact.*, **66**, 441.
Thompson, D'Arcy W. (1942): *On growth and form*. 2nd edition. Cambridge University Press, Cambridge.
Willis, R. A. (1948): *The pathology of tumours*. Butterworth, London.

RECURRENT PREGNANCY TOXAEMIA

BY

D. W. S. GORDON, M.D., F.R.C.S., M.R.C.O.G.
Senior Registrar
Queen Charlotte's Maternity Hospital

AND

M. R. FELL, M.M.S.A., M.R.C.O.G.
Consultant in Obstetrics and Gynaecology
Salisbury General Hospital
(Formerly Resident Obstetrician, Queen Charlotte's Maternity Hospital)

WHILST the aetiology of toxaemia of pregnancy remains obscured, any information about the clinical characteristics and future behaviour of this disease is likely to be of use for two reasons. First, one is in a stronger position to advise and manage these difficult cases if the tendency of toxaemia to repeat itself is known. Secondly, any small piece of evidence about the behaviour of toxaemia may, when fitted together with other facts, help elucidate its cause.

A critical review of previous work shows there to be a considerable diversity in the estimates of the risk of toxaemia occurring in subsequent pregnancies. This is coupled with a lack of definition of the criteria laid down to obtain these estimates. Furthermore, it was felt that some previous workers on this subject may have been accentuating certain aspects of the problem to elaborate a particular theory. In addition, most of the work on this subject had been done twenty-five years or more ago when the classification of pre-eclamptic toxaemia was less well defined than at present.

Under these circumstances, it was felt justifiable to enquire anew into this problem, and to try to assess, as accurately as possible, exactly what is the chance of pre-eclamptic toxaemia recurring. The theory that a renal lesion was the factor behind the recurrence of pre-eclamptic toxaemia has now been discarded, even by those who were its strongest exponents. However, the possibility that these women were getting toxaemia again because of an inherent tendency to develop essential hypertension has gained some support and, as a corollary to the main problem, it was decided to see if there was any evidence to substantiate this theory. Finally, an analysis was made of three factors which it seemed might influence the chance of recurrence—namely, the severity of the initial toxaemia, its duration, and time of onset in pregnancy.

HISTORICAL REVIEW

That toxaemia of pregnancy does tend to be a recurrent illness has been known for many years, but little work has been done on this side of the problem, compared to say the biochemical aspects. Young (1927) was one of the first in this country to describe and comment on the phenomenon of recurrent toxaemia. Careful perusal of his original article leads one to the conclusion that he thought the chance of toxaemia occurring again was in the region of 35 per cent. It was admitted that this figure did not reveal the total recurrence possibilities, and in 1929 he reported the results of a further enquiry. Fifty-one toxaemic patients had 84 subsequent pregnancies and "albuminuria" occurred in 44 of these, giving a figure of 52 per cent. This raises the fundamental point of how recurrence rate figures are to be expressed and it is obvious that there will be a difference between recurrence to next pregnancy, recurrence to any subsequent pregnancy and the overall recurrence rate, i.e., number of all the

pregnancies that occurred. It is unfortunate that it is not always entirely clear which rate an author is expressing.

It is interesting in relation to our own figures and to other people's results that Young found the overall pre-eclamptic toxaemia recurrence rate following eclampsia to be only 30 per cent —(18 toxaemias in 60 subsequent pregnancies).

Finally, he was also impressed by the high incidence of consequent abortion, stillbirth and accidental haemorrhage in pregnancies after a toxaemic one.

In the same year, Dr. Jessie Sym also analyzed a series of 93 cases. She found a recurrence rate (to any subsequent pregnancy) after pre-eclampsia of 55 per cent and after eclampsia of 40 per cent, and was the first to comment on this difference. Although her series may have contained some of Young's cases, they were in the main a different series, despite the co-incidental similarity in numbers (Dr. Sym—personal communication).

Gibberd has written more than once on this aspect of toxaemia, his first analysis being in 1928, when in 21 cases he found a recurrent toxaemia in 12 patients. In 1929 he reported on 51 originally healthy women who had had a toxaemic pregnancy, and of which almost exactly half had albuminuria in a subsequent pregnancy. It was at this time thought that a persisting renal lesion might result from toxaemia and 10 per cent of the original women were recorded as having developed signs of "chronic nephritis". In 1931 he presented a further series, showing amongst other things, that the recurrence rate (51 per cent) was related to the time that the toxaemic process was active. Thirty-six per cent had a recurrence if the toxaemia lasted for less than three weeks and 76 per cent recurred if the process lasted longer than this time. By 1934 he had collected 91 cases of whom 38 per cent had a recurrence of toxaemia in one or more subsequent pregnancies. It can be assumed that his cases of albuminuria of pregnancy are equivalent to pre-eclamptic toxaemia, but there remain 19 other cases segregated off because of a developing renal lesion, and these (like the 10 per cent described in his 1929 article) rather obscure his figure for possible recurrences.

Browne and Dodds (1939) described the results of the follow-up clinic at University College Hospital. By this time the question of hypertension persisting after toxaemia had been fully developed, and tended to overshadow all else in the follow-up of this condition. Thus, although a whole section of Browne and Dodds's paper is devoted to recurrent toxaemia, in which 114 patients who had 278 pregnancies were studied, the actual risk of recurrence is not stated or even mentioned in general terms. Defining hypertension as being above 130/70 mm. mercury, they found that 60 per cent of these patients had "hypertension" in the interval between pregnancies. Even the other 40 per cent did not escape as they were mostly "potential hypertensives", and this they believed accounted for the recurrence of toxaemia. However, Dodds (1957), gives a figure of 47 recurrences out of 144 cases of pre-eclamptic toxaemia (33 per cent) and 7 out of 46 eclamptics (15 per cent).

Gemmell, Logan and Benjamin (1954), by a retrograde mathematical analysis of a series selected primarily to show the overall incidence of toxaemia, calculated a recurrence rate, in primigravidae in their next pregnancy, of 15 per cent.

Gibson (1956), in an article again primarily concerned with the remote prognosis of toxaemia, found that in 116 toxaemic women, 43 had a recurrence in a subsequent pregnancy, giving an incidence of 37 per cent. He also found no evidence to suggest that the duration of the toxaemia influenced the chance of residual hypertension.

Finally, mention must be made of the work done in America by Chesley, Somers and Vann (1948). This is based on a follow-up of 103 women who had had eclampsia. Toxaemia of some degree occurred in at least one later pregnancy in 44 of these patients, giving a recurrence figure of 42·7 per cent—not 44·7 per cent as calculated in their article. In predisposing to a recurrence the following factors were listed: increasing age when the eclampsia occurred; the severity of hypertension in eclampsia; the duration of the toxaemia; the speed with which the blood pressure returned to normal and albuminuria disappeared after

Summary of Previous Results

Year	Author	No. of Cases	Percentage Recurrence	Type of Toxaemia
1929	Young	51	52	Pre-eclampsia
		42	30	Eclampsia
1928	Gibberd	21	57	Pre-eclampsia
1929	Gibberd	51	50	Pre-eclampsia
1931	Gibberd	—	51	Pre-eclampsia
1934	Gibberd	91	38	Pre-eclampsia
1929	Sym	93	48	Both
		42	40	Eclampsia
		51	55	Pre-eclampsia
1948	Chesley *et al.*	102	43	Eclampsia
1954	Gemmell *et al.*	—	15	Primiparas to next pregnancy
1956	Gibson	116	37	Both
1957	Dodds	144	33	Pre-eclampsia
		46	15	Eclampsia

delivery; and finally the weight/height ratio. The thoroughness of this report makes it particularly unfortunate that there had been no comparable work done by this centre on pre-eclampsia, which is after all the main problem we face in this country.

Material

The cases selected for this enquiry were taken from the Annual Report of Queen Charlotte's Hospital for the five years 1948–1952. During this period there were 17,562 deliveries and 996 cases of toxaemia occurred, and it is these patients who form the basis of this report.

The criteria for toxaemia was a blood pressure of 140/90 or over, together with the presence of albuminuria (contamination and urinary infection being excluded), and/or definite oedema. In fact, the combination of hypertension and oedema without albuminuria was very unusual; only 8 toxaemias were classified on this evidence alone. Albuminuria developing during labour was also not considered significant.

As it was desired to find the chance of recurrence in women who were perfectly healthy at the start of their pregnancy, all cases of essential hypertension in a woman who became toxaemic during her first pregnancy had to be excluded. Since the blood pressure may drop during the middle months of pregnancy, any case of "toxaemia" for which data was not available before the twentieth week also had to be left out. In fact, cases being referred late in pregnancy or emergency admissions were comparatively rare during the years studied. Taking into account the comprehensive analysis of "normal" blood pressure levels by Hamilton *et al.* (1954), it was felt reasonably safe to define essential hypertension, at this age group, as a level of 140/90 or over, present from the beginning of pregnancy.

In practice, it was found that accidental haemorrhage presented a more difficult problem and, unless it was clearly associated with toxaemia, it too, was excluded. However, its occurrence following toxaemia was noted and it will be discussed separately later, as will the incidence of abortion.

Letters were then sent to all the patients fulfilling the above criteria, asking if they had had any more children and whether these had been born at home or in hospital. If the confinement had been at home we assumed that toxaemia had not occurred; an assumption that we feel to be quite defensible. If the confinement had been in hospital, then that hospital was written to, asking for details of the pregnancy, with particular reference to the blood pressure readings and the development of toxaemia.

There were 209 cases in which there had been further traceable pregnancies after a toxaemic one and who were eligible under the criteria mentioned. Other letters to the number of 245 were sent out to mothers of which 105 had not had another pregnancy at the time of replying and 140 were untraceable. Each toxaemic pregnancy was then classified according to the severity of that toxaemia.

"Severe" were mothers who had eclampsia or alternatively a blood pressure in the range of 190/120 with six or more grams per litre of albumin. "Moderate" were mothers with a blood pressure around 160/100, and three to five grams per litre of albumin, and "mild" were below this level. It is agreed that this is only an approximation, but the cases could usually be classified without much argument.

Finally, the blood pressure range, particularly at the start, of all subsequent pregnancies was noted to see if there was any development of essential hypertension.

There were only 7 mothers who had eclampsia and subsequent traceable pregnancies and only one of these had pre-eclamptic toxaemia recurrently. As this group is too small to be of any significance it is not included in the final analysis of results, which therefore concern only recurrence after pre-eclamptic toxaemia.

There were only 10 cases of multiple pregnancy and it is of interest that toxaemia did not occur again in any of the subsequent pregnancies in this group.

Results

(a) *Risk of Recurrence in Any One Subsequent Pregnancy*

Type of Toxaemia	Yes	No	Per cent
Severe	21	15	59
Moderate	35	33	52
Mild	40	58	41
Total	96	106	47

(b) *Risk of Recurrence in Next Pregnancy*

Type of Toxaemia	Yes	No	Per cent
Severe	20	16	56
Moderate	32	35	48
Mild	37	62	37
Total	89	113	45

It can be seen from the above that, if pre-eclamptic toxaemia was to repeat itself at all, it almost always did so in the next pregnancy. Thus only 7 patients out of 113 who did not have a recurrence in the next pregnancy to the toxaemic one, developed toxaemia in a later pregnancy.

(c) *Recurrence Rate after Two Consecutive Toxaemic Pregnancies*

Thirty-three patients had a further recurrence. Thirteen patients did not have a further toxaemia=72 per cent chance of recurrence.

(d) *Recurrence Rate after Three Consecutive Toxaemic Pregnancies*

There were 9 cases, all of whom had a further recurrence=100 per cent chance of recurrence.

(e) *Type of Recurrence in Relation to Degree of Severity*

Each recurrent toxaemia was analyzed in relation to the preceding toxaemia. "Mild" cases recurred as a similar type in 85 per cent of cases. "Moderate" and "Severe" showed almost an even chance of recurring in a similar form.

(f) *Analysis of Blood Pressure at Subsequent Pregnancies*

Ninety-six "Positives" (i.e., patients developing a recurrent toxaemia); 8 had hypertension at beginning of a subsequent toxaemic pregnancy.

One hundred and six "Negatives"; 6 were hypertensive at subsequent pregnancies but did not get toxaemia.

(g) *Recurrence Rate in Relation to Time Toxaemic Episode was Present*

In this, and in the time of onset analysis, the cases of twin pregnancy were excluded, since they appear to behave rather as a group on their own. Of the remaining 192, there was sufficiently detailed information to be able to analyze 174 cases, both for the time factor and the date of onset of the toxaemia.

When the pre-eclamptic toxaemia settled and then appeared again, the total time it was present was calculated and the date of onset of the first episode taken.

Active Time in Weeks	One	Two	Three	Over Three
Recurrence ..	40	23	10	11
No recurrence ..	44	36	11	9

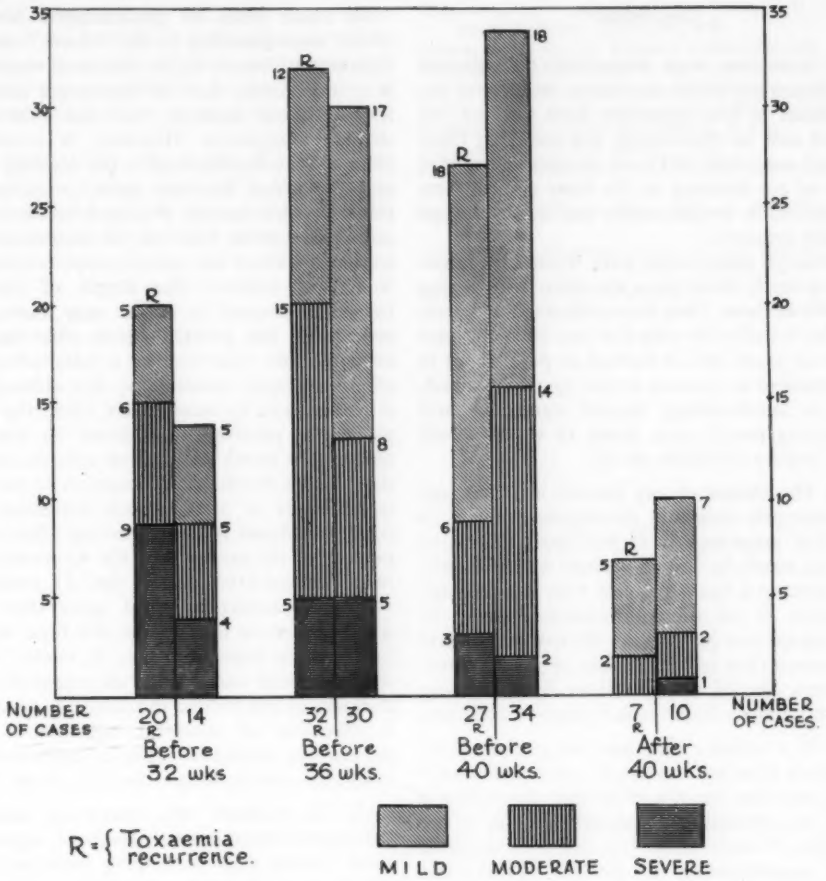


FIG. 1

If the "up to three weeks" group is compared to the "over three" (realizing the small number of the latter) the figure is 47 per cent compared to 55 per cent.

(h) *Recurrence Rate in Relation to Time of Onset of Toxaemia* (see Fig. 1).

(i) *Abortion Rate Following Toxaemia*

Information was available about 312 subsequent pregnancies and 48 miscarriages occurred in these pregnancies, giving a rate of just over 15 per cent. It did not appear that the risk of abortion was higher in the recurrent toxaemic group.

(j) *Accidental Haemorrhage*

As has been pointed out, this has only been included when there has been a definite antecedent toxic element, but there were three well defined cases in which toxic accidental haemorrhage appeared as a recurrent phenomenon in itself and these are included.

Discussion

"It is in some ways remarkable that, despite the close study which the clinical features of the toxaemias of late pregnancy have received, we should now be discovering, not only that there are still some fields left to us to explore, but that some of our teaching on the basic clinical facts has proved to be incomplete and in some ways actually unsound."

Although these words were written by James Young nearly thirty years ago there is still a ring of truth in them. They also underline the reason for this enquiry in which it has been the aim to be as exact and as factual as possible. It is not intended to theorize on the figures obtained, but, in summarizing, several significant and interesting points arise, many of which would seem worthy of further study.

(1) The chance of any woman who has had pre-eclamptic toxaemia developing it again in her next pregnancy is 45 per cent. That is to say that nearly half of all patients with toxaemia will develop it again the next time they become pregnant. If pre-eclamptic toxaemia occurs in two consecutive pregnancies the risk of a further recurrence rises to 72 per cent or nearly three-quarters. Should it occur three times running then toxaemia a fourth time is almost a certainty.

(2) If a woman who has had pre-eclamptic toxaemia does not develop it again in her next pregnancy then the risk of her ever developing it again in subsequent pregnancies is only 6 per cent (i.e., 7 out of 113). This risk is of the same order approximately as the risk of toxaemia occurring in a patient who has never previously had it.

(3) It is suggested that pre-eclamptic toxaemia developing in association with multiple pregnancy behaves differently and merits consideration as a separate problem. Thus there were 10 cases of twins, all of whom developed signs of pre-eclamptic toxaemia for the first time during the twin pregnancy, but none developed it in any subsequent pregnancy. It may be that toxaemia associated with multiple pregnancy does not carry the same risk of recurrence in future pregnancies as does toxaemia occurring with a single pregnancy.

(4) Those cases of pre-eclamptic toxaemia which were classified in the "severe" category appeared to have a higher chance of recurrence. It is unfortunate that the figures are too small for statistical analysis, but the evidence is strongly suggestive. However, it cannot be claimed that severity itself is the deciding cause, and an attempt has been made to analyze two other possible factors. It cannot be denied that eclampsia carries less risk of recurrence than toxaemia without fits, and this apparent anomaly is full of interest. The length of time the toxaemic process is active may have some bearing on this point, if, as is often the case, eclamptic fits supervene on a fulminating type of pre-eclamptic toxaemia, so that although this is toxaemia in its most severe form, the whole process is relatively short-lived. In this connexion it is worth noting that with the present-day trend towards early induction in the more severe cases of pre-eclamptic toxaemia, there is the likelihood of a diminishing effect on the severity of the process and the recurrence rate; thus Gibberd (1931) could find 21 patients in which the toxaemia lasted more than three weeks compared to 36 under this time, whereas in this series there were only 20 in the "over 3 weeks" group and 154 in the remainder. The duration of the process in relation to recurrence is therefore of doubtful significance under present-day conditions when comparatively few toxaemias are prolonged for over three weeks.

(5) No evidence was found on analyzing subsequent blood pressure levels to suggest that these women were developing recurrent toxaemia because of the associated onset of essential hypertension.

(6) The time of onset of the toxaemic process is of doubtful significance especially as a higher proportion of the "severe" cases occurred in the earlier onset group.

This survey was conducted by a retrospective investigation and has all the disadvantages associated with this. The replies received, however, are not likely to be selected in any way and it was possible by studying a 5-year period to obtain a larger series than any yet published. It is appreciated that there are many other factors that could well be investigated but it is

hoped that this survey will both help future analysis of the behaviour of toxaemia as well as stimulate enquiry into the fundamental question as to why toxaemia should, in any event, show such a well-marked recurrent tendency.

We would like to thank the Board of Governors of Queen Charlotte's Hospital for bearing the cost of this enquiry and also the Records Department staff for their kind help.

References

Browne, F. J., and Dodds, G. B. (1939): *J. Obstet. Gynaec. Brit. Emp.*, **46**, 443.

Chesley, L. C., Somers, W. H., and Vann, F. H. (1948): *Amer. J. Obstet. Gynec.*, **56**, 409.

Dodds, G. B. (1957): Personal communication.

Gemmell, A. A., Logan, W. P. D., and Benjamin, B. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 458.

Gibberd, G. F. (1928): *Proc. R. Soc. Med.*, **21**, 831.

Gibberd, G. F. (1929): *Brit. med. J.*, **1**, 674.

Gibberd, G. F. (1931): *Lancet*, **2**, 524.

Gibberd, G. F. (1934): *J. Obstet. Gynaec. Brit. Emp.*, **41**, 23.

Gibson, G. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 833.

Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., and Sowry, G. S. C. (1954): *Clin. Sci.*, **13**, 11.

Sym, J. C. B. (1929): *Lancet*, **2**, 698.

Young, J. (1927): *J. Obstet. Gynaec. Brit. Emp.*, **34**, 279.

Young, J. (1929): *Proc. R. Soc. Med.*, **22**, 314.

PRIMARY AMENORRHOEA AS A MANIFESTATION OF PELVIC TUBERCULOSIS

BY

H. E. REISS, M.A., B.M., M.R.C.O.G.

Assistant to the Obstetric Unit

University College Hospital, London

AMENORRHOEA is a well-recognized accompaniment of tuberculosis of the female genital tract, though its incidence is variable. Thus, Schröder (1921) found it in 13 of 44 cases of endometrial tuberculosis; Liljedahl and Rydén (1951) encountered it only 4 times in their 148 cases; whilst Sutherland (1956) had 22 such patients in his series of 200. Nearly always this is a secondary amenorrhoea, and primary amenorrhoea must be considered a rare manifestation of this disease. Although endometrial tuberculosis is included by Oastler and Sutherland (1956) in their classification of the causes of primary amenorrhoea, only 3 such cases have been described in this country—2 by Sutherland (1943, 1956) and 1 by Netter and Netter-Lambert (1952). The diagnosis in these cases was made by curettage, the curettings being composed entirely of tuberculous granulation tissue and devoid of functioning glands. Other cases of tuberculous primary amenorrhoea, due to complete destruction of the uterine endometrium and its replacement by a fibrino-purulent exudate, are described by Heesch (1928), Dworzak (1931), Schmidt and Faulkner (1947), and Philipp (1953).

Apart from this type of amenorrhoea, associated with total destruction of the glands of the endometrium, there exists a second variety in which intra-uterine adhesions prevent the escape of the menstruum; in these cases, provided the original inflammation has not completely destroyed the endometrial glands, retrograde menstruation is liable to occur.

Two cases of pelvic tuberculosis, associated with the formation of a fibromuscular bar across the lower pole of the uterine cavity, and presenting clinically as cases of primary amenorrhoea, have been seen in recent years at University College Obstetric Hospital.

CASE REPORTS

Case 1

Mrs. N., a secretary, aged 35 years, was admitted to University College Obstetric Hospital in October, 1952. Her chief complaints were primary amenorrhoea and a mild degree of deep dyspareunia. She had no discharge. She had been married for 10 years, had a normal libido, and coitus was, on the whole, satisfactory. She had suffered for many years from acne. Apart from measles in childhood, there was no past history of illness. The family history was uninformative: the mother was alive and well but nothing was known about the present state of the father; she had three unmarried sisters i.. whom menstruation was normal. Since the age of 16 years, Mrs. N. had consulted several doctors and had been treated unsuccessfully with gonadotrophins, oestrogens, ethisterone and thyroid. Three years previously pelvic examination had revealed a cystic mass in the pouch of Douglas.

On examination she appeared a healthy, well-developed woman with normal secondary sex characteristics. The heart and lungs were normal, and the blood pressure 136/84 mm. Hg. Abdominally there were no abnormal findings.

Pelvic examination revealed a normal vulva, clitoris and vagina. The uterus was retroverted and normal. The cervix was healthy and pointed downwards and forwards. There was a cystic swelling, the size of an orange, not freely mobile, in the pouch of Douglas.

Special investigations revealed the blood count and urine to be normal. The 17-ketosteroid excretion was 6·8 mg. in 24 hours. The vaginal smear was reported by Dr. G. I. M. Swyer as fully oestrogenized.

Examination under anaesthesia confirmed the pelvic findings. The uterine sound was held up by an obstruction at 1½ inches (3·75 cm.). The cervical canal was dilated, but no curettings were obtainable.

Laparotomy was performed 3 days later under general anaesthesia, through a midline subumbilical incision. There were multiple pelvic adhesions, a small retroverted uterus, and a cystic mass behind and attached to the uterus. The tubes and ovaries were not separately identifiable. The uterus and mass, including the appendages, were removed. The appendix, which appeared healthy, was also removed and the abdomen closed. The post-operative course was uneventful. In view of the pathological findings a chest X-ray was done one week after operation: there was obliteration of the right costophrenic angle, indicative of old pleurisy, and a small healed focus was found in the left infra-clavicular region. A further X-ray, 3 months later, showed no change. Five years later her family doctor, Dr. W. C. Robinson, reports that the patient is alive and in good health.

Pathological Report (Dr. P. E. Hughesdon). "The mass behind the uterus resolved itself, on dissection, into bilateral tubo-ovarian cysts: the right the size of a golf ball, the left the size of an orange. The uterus is small and has a bar across the cavity, dividing it completely into two. Below the bar the cavity and wall look normal; above it contains pale chocolate-coloured pus."

Histology. "Normal cervix and isthmus up to the obstruction. Above this the uterus is lined by tuberculous granulation tissue, though there is still a little surface and gland epithelium left. The tubes show tuberculosis and non-specific salpingitis. The right ovary is normal in itself; there is a mild peri-oöphoritis and the attached cyst is lined by tubal epithelium. The left ovary shows a similar appearance and the cyst attached to it is lined by non-specific flattened epithelium. Ziehl-Neelsen stains negative."

Comment. The finding of tuberculosis in this case was unexpected. There was almost complete destruction of the endometrium, and atresia of the lower pole of the uterine cavity. The pelvic adhesions were probably the result of the old tuberculous infection. There was no evidence of retrograde menstruation: a not surprising finding in view of the almost total absence of endometrium.

Case 2

Mrs. P., a state registered nurse, aged 27 years, was first admitted to University College Obstetric Hospital in July, 1956, for investigation of primary amenorrhoea. She had married 4 months before, and was experiencing severe deep dyspareunia. During the previous 6 weeks she had had repeated attacks of lower abdominal pain, in the midline and the left iliac fossa.

Past history. Although she had never menstruated, she had experienced, since the age of 17 years, regular monthly attacks of lower abdominal pain, lasting 1 to 2 days, and worse on the right side. Sometimes these attacks were accompanied by a white mucoid vaginal discharge. At the age of 18 years she had had hormone treatment by mouth, with no effect. Three years before admission, she had been admitted to another hospital on account of an acute attack of pain in the right iliac fossa. At laparotomy multiple pelvic adhesions were found; there was a right pyosalpinx and thickening and occlusion of the left tube; the right ovary was cystic and twice its normal size, the left appeared normal. The uterus was small and normal. Old adhesions were noted in the region of the appendix and there was a small calcified gland on the posterior pelvic wall. Partial right salpingectomy, resection of the right ovarian cyst and appendicectomy were performed. A dilatation and curettage was attempted at the end of the operation, but the dilators only passed 1 inch (2·5 cm.) and only scanty curettings were obtained. Histology revealed extensive chronic tuberculosis of the right tube. The curettings showed normal endocervical epithelium with sub-epithelial infiltration by plasma cells. Pus from the pyosalpinx grew *Staphylococcus pyogenes*. No tubercle bacilli were found on direct staining or on culture.

X-ray examination of the chest revealed a doubtful focus in the left upper zone, and the appearance did not change during the next year. Following this operation the patient had been treated for 3 months with streptomycin and para-aminosalicylic acid.

Apart from this, the past history included only measles, mumps, and chicken pox in childhood.

Family history. Her father had died in 1937 from pulmonary tuberculosis. She was then 8 years old.

On examination she appeared a healthy, slim and attractive young woman with normally developed secondary sex characteristics. The heart and lungs were normal and the blood pressure 120/80 mm. Hg. In the abdomen there was a midline sub-umbilical scar and some tenderness on deep palpation in the left iliac fossa, but no other abnormality. Pelvic examination revealed a normal vulva, clitoris and vagina. The uterus was ill-defined, anteverted, small, tender and not freely mobile. There was a tender mass, the size of a hen's egg, in the left fornix. The cervix pointed down and backwards and its mobility was also limited. There was moderate excitation pain. Speculum examination was normal.

Special investigations revealed normal blood counts, sedimentation rate and chest X-ray. Microscopy and culture of the urine (including culture for tubercle bacilli) showed no abnormality. The report on the vaginal smear (Dr. G. I. M. Swyer) was as follows: "Cornified cells 5 per cent; pseudo-cornified cells 5 per cent; intermediate cells 87 per cent; karyopyknotic non-cornified cells 3 per cent. Leucocytes +++. Bacteria +++. This could be a progestational smear; it is certainly not significantly hypo-oestrogenic."

Examination under anaesthesia was carried out on 24th July, 1956. The previous pelvic findings were confirmed. It was impossible to pass a uterine sound farther than 1½ inches (3·75 cm.) from the external os, and there appeared to be complete occlusion rather than a stricture at this level.

The paraffin block of tissue from the right pyosalpinx removed in 1954 was obtained for re-examination by Dr. P. E. Hughesdon who found it showed many typical tubercles, a few with incipient caseation.

It was considered that in view of the negative results from all investigations further treatment with anti-tuberculous drugs was not at present indicated, and the patient was discharged.

Second admission. Mrs. P. was re-admitted in January, 1957, complaining of lower abdominal pain, present at all times, but worse at regular monthly intervals. Dyspareunia was severe enough for her to avoid coitus. As her symptoms were interfering with her professional and married life, she requested surgical treatment, accepting the fact that reproduction was unlikely in any case. Abdominal and vaginal findings at this time were unchanged. Pre-operative treatment with streptomycin 0·5 g. twice daily intramuscularly and oral iso-nicotinic acid hydrazide 100 mg. twice daily was started 1 week before operation and continued for 2 weeks post-operatively.

Operation. On 9th January, 1957, the abdomen was opened, under general anaesthesia, by a midline sub-umbilical incision, excising the old scar. The uterus and appendages were obscured by adhesions; the rectum and sigmoid colon were adherent to the back of the uterus and both broad ligaments. Dissection revealed a cystic left ovary, the size of a table tennis ball, and a moderate sized left hydrosalpinx. There was a small right hydrosalpinx in the remaining portion of the right tube and a cystic right ovary, closely adherent to the right ureter. Total hysterectomy, partial right salpingo-oöphorectomy and left salpingo-oöphorectomy were performed, and the abdomen closed. Post-operative recovery was uneventful. Since the operation the patient has been well, with no menopausal disturbances and completely relieved of all pain.

Pathological Report (Dr. P. E. Hughesdon). "The specimen consists of a complete uterus (7×6×3 cm.) of normal size, with a band of fibromuscular appearance across the isthmus: above this the cavity contains altered blood: a left-sided haematosalpinx, closed distally, of 2 cm. maximum diameter; and bilateral ragged adnexal masses (Right 3×4×5 cm.; Left 3×4×5·5 cm.) presumably ovaries and broad ligaments fused."

Histology. "The uterus shows a mildly hyperplastic endometrium without tubercles or siderocytes. The isthmic band is similar in structure to myometrium. The interstitial tubal regions show blood in the lumen, much surface papillation, and numerous subjacent mural diverticula (salpingitis interstitiale nodosa): no tubercle is seen but Schaumann bodies are present. The left distal tube contains blood and shows a rather indolent tuberculous salpingitis, with Schaumann bodies. A single Ziehl-Neelsen stain was negative. The right ovary shows only non-specific peri-oöphoritis. The left ovary shows the same, but also contains a central irregular cavity lined mainly by hyalinizing chronic siderotic granulation tissue, and in a few places by epithelium lying on a narrow loose stromal seam containing a few siderocytes: this is almost certainly a long-standing endometrial cyst."

Comment. Schaumann bodies, according to Burne (1953) are an indication of previous tuberculous infection. This case differs from Case 1 in as much as the endometrium was not completely destroyed by tuberculosis: the fibrous bar across the lower uterine pole prevented the escape of menstrual fluid and retrograde menstruation, accompanied by monthly molimina, occurred.

Discussion

The association of primary amenorrhoea with a mechanical obstruction, such as atresia of the lower pole of the uterine cavity, was first described by Rieck (1909) in 2 cases. Menstrual molimina were present in both patients and in both he demonstrated a muscle layer, 1 cm. thick, separating the endometrial cavity from a normal cervical canal. The first patient's father had died of tuberculosis. She had a right tubo-ovarian mass, multiple pelvic adhesions, and yellow caseous material in the endometrial cavity. The second patient had multiple pelvic adhesions, a right haematosalpinx and unclotted blood in the endometrial cavity. In both cases Rieck induced menstruation by the creation of a utero-vaginal fistula, ingeniously constructed and by-passing the cervix. Histological proof of the origin of the condition was not obtainable as the uterus was not removed in either patient.

Eden (1912) described a case of primary amenorrhoea in a patient with severe menstrual molimina; at laparotomy bilateral pyosalpinges

were found. The ovaries were healthy and functioning. Sub-total hysterectomy revealed a normal uterus lined with thin endometrium and microscopy showed multiple giant cell systems in the tubes, indicative of tuberculosis. It is tempting to speculate that atresia of the lower part of the uterine cavity might have been found if total, rather than sub-total, hysterectomy had been performed.

Schiffmann (1914) first provided real proof of atresia of the lower part of the uterine cavity in 2 cases of pelvic tuberculosis. Both patients presented with primary amenorrhoea associated with menstrual molimina. Following hysterectomy, histological examination of the areas of atresia showed them to be composed of granulation tissue with many epithelioid and giant cells. He concluded that the atresia was the result of a severe ulcerative process, which had healed with the formation of granulation tissue, and that its site was evidence of the susceptibility of uterine endometrium and resistance of cervical mucosa to tuberculosis. In this connexion Hughesdon's (1957) observation, that endometrial tuberculosis frequently affects the region of the uterine isthmus with particular severity, is highly relevant.

More recently Netter *et al.* (1954, 1955) have reported 3 cases of primary amenorrhoea in which intra-uterine adhesions or atresia, apparently (though not conclusively proved) of tuberculous origin, were demonstrated. Similar cases are recorded by Musset and Salomon (1955), Gaudefroy (1956) and Solal (1957).

These intra-uterine atresiae and adhesions are symptomatically and macroscopically similar in all respects, apart from the presence of primary amenorrhoea, to those of amenorrhoea traumatica described by Asherman (1948). In this condition, the patients ovulate, but fail to menstruate, and passage of a sound invariably reveals a block at the level of the internal os. The stenosis or atresia usually follows curettage for secondary post-partum haemorrhage, missed abortion, or incomplete abortion. This is a not uncommon condition in some countries (France, Algiers, Belgium, Israel) and several series of cases are reported by Hald (1949), Halbrecht (1953), Demiot (1955), Solal *et al.* (1956), Gaudefroy (1956) and Limage (1956).

The apparent rarity or even non-existence of traumatic amenorrhoea in this country is difficult to explain, though the British preference for digital evacuation of the uterus or the use of a blunt curette, which will not penetrate to the muscle layer, may well be relevant.

The precise mechanism of production of intra-uterine atresiae, whether tuberculous or traumatic in origin, is not known. Schiffmann (1914) considered that adhesions and subsequent cicatrization of granulation tissue occurred at the level of the internal os between adjacent surfaces, in close contact, deprived of their epithelial lining. Asherman (1948) considered that tetanic contractions of the circular muscle fibres at the level of the internal os lead to a spastic stricture which in time becomes organic and thus permanent.

It will depend on the exact site and extent of the intra-uterine atresia whether enough functioning endometrium remains to menstruate; if so, retrograde menstruation occurs as in Case 2 here described, and as also reported by Rieck (1909, 1933), Hald (1949), and Netter *et al.* (1955).

Conclusion

Primary amenorrhoea is a rare manifestation of pelvic tuberculosis. This is not unexpected in view of the work of Barns (1955) who showed that primary tuberculous infection before puberty only rarely results in dissemination of the disease to the pelvic organs. Most women who have pelvic tuberculosis acquired their primary complex at or after puberty.

The possible causes of amenorrhoea in cases of pelvic tuberculosis are threefold: (1) destruction of ovarian tissue by parenchymatous infection; this must be extremely rare, but is reported by Schröder (1921); (2) destruction of all gland-bearing endometrium; (3) atresia of the lower part of the uterine cavity. The last two varieties are seen in patients who have normally-developed secondary sex characteristics, often experience menstrual molimina, show oestrogenic activity in their vaginal smears, and fail to have withdrawal bleeding after hormone administration. Menstrual molimina are apt to be particularly marked in the

patients who experience retrograde menstruation. Only hysterosalpingography or the passage of a uterine sound will distinguish between these two varieties, and their existence proves the futility of persistent hormone therapy in cases of primary amenorrhoea not fully investigated.

For the cases where no endometrium, or only scanty tissue, is obtained at curettage, even though there is no obstruction to the uterine sound, Borrell and Rydén (1954) describe the following diagnostic aid: 5 mg. of intramuscular oestradiol monobenzoate is given daily for 6 days: further curettage may then reveal more endometrial tissue to facilitate the diagnosis of tuberculosis.

If atresia is found and is not of the traumatic variety described by Asherman (1948), it is doubtful whether any treatment, except the creation of a utero-vaginal fistula as described by Rieck (1909) will induce menstruation. Attempts to open up the area of atresia by passage of bougies, and to maintain it by the insertion of stem pessaries or polythene tubing, have been unsuccessful in the non-traumatic group. In any case the desirability of such operative procedures in a patient with old tuberculous disease of the pelvis is highly questionable. Radical surgery is indicated if symptoms are severe enough to call for intervention and the disease is inactive and no longer responds to anti-tuberculous drugs.

Summary

The literature on primary amenorrhoea in association with pelvic tuberculosis is reviewed. Two varieties are recognized: one in which there is complete destruction of the glandular epithelium of the uterus; the other in which intra-uterine atresia or adhesions are responsible for the amenorrhoea. Two cases of the latter variety are described and it is shown that retrograde menstruation may occur in cases of atresia in which there is not at the same time total destruction of the endometrium.

Acknowledgments

I am indebted to Miss Josephine Barnes and Professor W. C. W. Nixon for permission to report Cases 1 and 2 respectively; and to Dr. G. I. M. Swyer and Dr. P. E. Hughesdon for their reports and suggestions.

References

Asherman, J. G. (1948): *J. Obstet. Gynaec. Brit. Emp.*, **55**, 23.
Barns, T. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 162.
Borrell, U., and Rydén, A. B. V. (1954): *Acta obstet. gynec. scand.*, **33**, 327.
Burne, J. C. (1953): *J. Path. Bact.*, **65**, 101.
Demiot, M. (1955): *C.R. Soc. franç. Gynéc.*, **25**, 420.
Dworzak, H. (1931): *Zbl. Gynäk.*, **55**, 2030.
Eden, T. W. (1912): *Proc. R. Soc. Med.*, **5**, Obstet. Gynaec. Sect., 265.
Gaudefroy, M. (1956): *C.R. Soc. franç. Gynéc.*, **26**, 483.
Halbrecht, I. (1953): *Fertil. Steril.*, **4**, 272.
Hald, H. (1949): *Acta obstet. gynec. scand.*, **28**, 169.
Heesch, O. (1928): *Zbl. Gynäk.*, **52**, 541.
Hughesdon, P. E. (1957): Personal communication.
Liljedahl, S. O., and Rydén, A. B. V. (1951): *Acta obstet. gynec. scand.*, **30**, 359.
Limage, J. (1956): Personal communication. Bruxelles.
Musset, M. R., and Salomon, Y. (1955): *C.R. Soc. franç. Gynéc.*, **25**, 352.
Netter, A., Lambert, A., Kahn, J., and Montbazet, M. (1954): *C.R. Soc. franç. Gynéc.*, **24**, 165.
Netter, A., Musset, R., Lambert, A., Salomon, Y., and Montbazet, G. (1955): *Gynéc. Obstét.*, **54**, 19.
Netter, A., and Netter-Lambert, A. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 744.
Oastler, E. G., and Sutherland, A. M. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 355.
Philipp, E. (1953): *Arch. Gynäk.*, **183**, 247.
Rieck, A. (1909): *Münch. med. Wschr.*, **56**, 559.
Rieck, A. (1933): *Zbl. Gynäk.*, **57**, 2665.
Schiffmann, J. (1914): *Arch. Gynäk.*, **103**, 1.
Schmidt, R. T., and Faulkner, R. L. (1947): *Amer. J. Obstet. Gynec.*, **53**, 695.
Schröder, R. (1921): *Zbl. Gynäk.*, **45**, 43.
Solal, R., Jude, —., and Palvadeau, —. (1956): *C.R. Soc. franç. Gynéc.*, **26**, 389.
Solal, R. (1957): *Presse. méd.*, **33**, 774.
Sutherland, A. M. (1943): *J. Obstet. Gynaec. Brit. Emp.*, **50**, 161.
Sutherland, A. M. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 161.

LIVING BIRTHS FOLLOWING DRUG THERAPY FOR INFERTILITY ASSOCIATED WITH PROVEN GENITAL TUBERCULOSIS

BY

ALBERT A. EARN,* M.D., M.Sc.(Med.), M.R.C.O.G.
Registrar, Obstetrics and Gynaecology
Leicester General Hospital, Leicester

THE object of this paper is to report two successful full-time pregnancies following proven genital tuberculosis associated with infertility. The patients were treated with Streptomycin and Isonicotinic acid hydrazide (INAH). This we believe to be the first record of confinements at term following treatment with this combination of drugs. A consideration of the present knowledge of genital tuberculosis in relation to infertility will follow in view of the evidence accumulating in the literature.

CASE HISTORIES

CASE 1

Mrs. S.L.H. (G-2645), aged 23 years, married 3 years, was first seen in the gynaecological clinic on 21st January, 1955.

The patient complained of infertility present for 2½ years, and lassitude present for 2 years.

She had been unable to conceive during the past 2½ years. Satisfactory coitus occurred 2 to 3 times weekly. Contraceptives were not used.

Lassitude had gradually developed during the last 2 years. She thought she was losing weight but had no idea of the amount of weight loss.

Menstruation began at the age of 13 years. The menses lasted 7 days and recurred every 2 to 6 weeks. The loss was slight to heavy. Her last menstrual period began 10 days ago. There was no metrorrhagia, dysmenorrhoea or leucorrhoea.

She had always been in good health. She had served in the Women's Royal Naval Service during 1950.

There was no history of any known tuberculosis or chronic respiratory disease in the family or among her relatives or friends.

Examinations

Mrs. H. was a healthy-looking young woman showing no apparent loss of weight. No abnormalities were detected in the lungs or the abdomen on clinical examination. Pelvic examination showed an elastic rugose clean vagina. The cervix was nulliparous, pink, mobile and not tender. The uterine body felt slightly enlarged for a nullipara; but was anteverted, regular in outline, mobile and not tender. A sound was passed for 3 inches (7·5 cm.) into the uterine cavity. The ovaries were palpable, free on the side-wall of the pelvis, not enlarged or tender. The oviducts were not palpable. No masses or abnormalities were detected on bimanual recto-vaginal examination.

A chest X-ray showed no evidence of pulmonary tuberculosis. The blood sedimentation rate was 2 mm. an hour. The haemoglobin estimation was 82 per cent (12·8 g.). The white blood cell count was 7,400 per ml., and a differential count showed 53 per cent polymorphs, 45 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles. Urine examination showed no macroscopic or microscopic changes. Culture of the urine on Löwenstein's media showed no growth after 6 weeks incubation. A Mantoux test 1/1,000 was positive for tuberculosis.

The patient was advised to have a premenstrual uterine curettage, to secure sufficient endometrium for various investigations. Meantime, she was to keep a basal body temperature chart and to send her husband for a semen analysis.

She was admitted 4th March, 1955. The history remained unchanged. Her last menstrual period began 23 days ago. Examination under anaesthesia confirmed the previous findings in the pelvis. Dilatation and curettage of the uterus procured smooth pink endometrium totalling in diameter ¾ of an inch (2 cm.).

Investigations

Serial section of the entire block of endometrium revealed no tuberculous lesion. The endometrium was in the proliferative phase. Ziehl-Nielson stains of the tissue sections showed no alcohol acid-fast bacilli.

* Home address: 414 Atlantic Avenue, Winnipeg, 4, Canada.

Endometrial suspension was cultured on Löwenstein's medium. *Mycobacterium tuberculosis* was not isolated after 6 weeks incubation (18th April, 1955). A guinea-pig inoculated intramuscularly with endometrial suspension was killed after 7 weeks (25th April, 1955) and found to have tuberculosis. Ziehl-Nielson stained smears of the tissue showed alcohol acid-fast bacilli.

A diagnosis of proven tuberculous endometritis was made.

The patient's basal body temperature chart showed a thermal plateau for 2 weeks premenstrually in each cycle.

Meantime, her husband was examined and found to be healthy. His semen analysis was normal and gave a count of 251 million spermatozoa per ml.

The patient was admitted for treatment on 2nd June, 1955. Symptoms and signs remained unchanged. Pulmonary and urinary investigations revealed no evidence of tuberculosis. The treatment given was a daily intramuscular injection of Streptomycin 1 g. and orally INAH 300 mg. in divided doses. Therapy was continued for 4 months. The patient was discharged on 30th September, 1955.

She attended the clinic on 4th November, 1955. She looked and felt well. Menstruation had changed to 6 days every 5 to 6 weeks. The loss had decreased in amount. Pelvic examination showed some vague tenderness in the right tubo-ovarian region. No abnormalities were palpable. The uterus was nulliparous in size and its cavity had decreased to 2¾ inches (7 cm.) in length. An endobiopsy was taken for histological and bacteriological investigations.

Histological examination showed the endometrium in the proliferative phase and no pathology. A guinea-pig which had been inoculated with endometrial suspension was killed after 6 weeks and showed no evidence of tuberculosis.

She was seen again 6th January, 1956 (3 months after treatment). Her menses had changed to 5 to 7 days every 29 days. Mild congestive dysmenorrhoea had developed for 2 days before each period. Pelvic examination revealed no abnormalities. The left ovary felt slightly larger than the right ovary. Her blood sedimentation rate was 5 mm. in one hour. The patient was trying to become pregnant.

Pregnancy. Mrs. H. was next seen 7th September, 1956. Her last normal menstrual period began 9th May, 1956 (8 months after treatment). She was well and had no complaints. Examination showed an anteverted cyetic uterus consistent in size with 16-weeks amenorrhoea. Her pregnancy continued uneventfully.

Labour. Labour started spontaneously on 25th February, 1957 (40½-weeks pregnancy). She was delivered successfully after 18 hours and 33 minutes. The blood loss was about 2 ounces (60 ml.). The grossly normal placenta complete with its cord and membranes was sent for histological and bacteriological investigations. The healthy and normal infant weighed 7 pounds 8 ounces (3,400 g.).

Puerperium. The mother was apyrexial throughout the puerperium. The baby was fully breast-fed. It was inoculated with B.C.G. on 28th February, 1957. Ten days post-partum, pelvic examination of the mother showed an anteverted involuting uterus with a closed cervix. No abnormalities were detected in the adnexae. The mother and baby were discharged home the same day.

Mrs. H. and her baby attended the postnatal clinic 10th April, 1957 (10 weeks post-partum). Pelvic examination of the mother showed a multiparous involuted anteverted uterus. No pelvic pathology was detected. The oviducts were not palpable. The mother was asked to return in 3 months for a follow-up endobiopsy.

The infant was well and gaining weight. It was bottle-fed as the mother's breast milk had become inadequate. The baby had become immunized from the B.C.G. vaccination.

Histological examination of the placenta showed no evidence of tuberculosis. Ziehl-Nielson stained tissue sections revealed no alcohol acid-fast bacilli. Löwenstein's medium inoculated with placental suspension showed no growth after 6-weeks incubation. A guinea-pig killed 6 weeks after inoculation with placental suspension showed no evidence of tuberculosis.

Second Pregnancy. The patient attended the follow-up clinic on 10th July, 1957. She had missed 3 periods and thought she was pregnant. Pelvic examination showed a 12-weeks size cyetic uterus. No other abnormalities were detected.

Case 2

Mrs. W.U. (G-8116) was first seen in the gynaecological clinic on 30th September, 1949, when she was single and aged 16 years.

The patient complained of irregular heavy periods with clots, present for the previous 12 months, and hypogastric and sacral dysmenorrhoea also present for 12 months.

The symptoms developed one year ago following an appendicectomy.

For the past 12 months her menses had changed to 3 to 4 days in every 6 to 7 weeks. Previously, since the onset of menstruation at the age of 14½ years, her periods occurred for 5 to 7 days in every 28 days.

The hypogastric and sacral ache began with the onset of each period and lasted for 7 days, although menstruation ceased after 4 days.

An intussusception was surgically corrected at the age of 5 weeks. Her appendix was removed in August, 1948, elsewhere. The serosa of the appendix showed some injection. No pathology was noted in the pelvis or the abdomen.

The patient's lungs had been X-rayed for the first time on 13th August, 1943; as she was a contact of her sister who had recently been found to have tuberculosis. The sister was a nurse in a chest hospital. The report on the patient's lungs and those of the rest of her family revealed no evidence of pulmonary tuberculosis.

Examination showed a healthy looking adolescent. Her neck, lungs and abdomen showed no abnormalities on clinical examination. A vague tender mass in the region of the right fornix was palpable *per rectum*.

Radiographs of her lungs showed no evidence of tuberculosis. X-rays of her pelvis showed no abnormalities.

The patient was advised to come in for a proper pelvic examination under anaesthesia and for diagnostic uterine curettage. She refused.

Mrs. U. was again referred to the clinic on 10th August, 1954. She was now 22 years old and had been married for 2 years.

The patient complained of: (1) infertility, (2) pain, (3) weight loss, (4) acyclic excessive menses.

Infertility was present since her marriage 2 years ago. No contraceptives were used. Satisfactory coitus occurred 3 times weekly.

The previous intramenstrual pain had developed into a constant ache during the past 1½ years. Left iliac fossa ache appeared at the same time and occurred after each coitus.

She had lost 2 stones in weight during the past year and noted that night sweats had been recurring during the same time.

Her menstrual cycle had altered. Menstruation continued for 7 to 9 days in every 4 to 7 weeks.

In 1951 she had joined the Home Help Service. A routine chest film was taken on 2nd February, 1951, and showed no evidence of tuberculosis. She had a routine Mantoux test 1/1,000 at that time which was negative. As members of the Home Help Service may come into contact with tuberculous cases, it was the usual practice to recommend B.C.G. vaccination to any employee who had a negative tuberculin test. Because of this and the family history of tuberculosis, Mrs. U. was given B.C.G. vaccination on 14th April, 1951. Vaccination was successful and her follow-up tuberculin test on 23rd June, 1951 was positive. A follow-up X-ray of her chest on 30th January, 1952 showed no evidence of pulmonary tuberculosis.

In August, 1952, Mrs. U. was admitted elsewhere for suspected meningitis. Her spinal fluid showed no abnormalities. It was not cultured. She was sent home untreated and well after 15 days.

Examinations

Mrs. U. was a thin young adult woman. Her chest and abdomen showed no clinical abnormalities. On pelvic examination, the vagina was healthy; the cervix was pink and nulliparous; the uterine body was anteverted, regular, firm, mobile and not tender, but elongated for a nullipara; the left oviduct was palpable, mobile and diffusely enlarged; the right oviduct was not palpable. The utero-sacral ligaments and parametria were elastic, uniform and not tender.

The patient was advised to have a curettage to secure endometrium for histological and bacteriological investigations.

Mrs. U. was admitted on 2nd February, 1955 due to her delay of 5 months. The symptoms and signs remained unchanged, with the exception of the enlarged left oviduct which was now not palpable.

Lung radiographs showed no tuberculosis. The blood sedimentation rate was 3 mm. in one hour; the haemoglobin was 91 per cent; the white blood cell count was 8,000 per ml., and the differential blood count showed 73 per cent polymorphs, 22 per cent lymphocytes, and 5 per cent monocytes.

Examination under anaesthesia confirmed the clinical findings. A sound was passed into the uterus for 3¼ inches (82 mm.). Uterine curettage obtained scanty endometrium totalling ¼ inch (6 mm.) in diameter plus curetted blood. This material was sent for histological and bacteriological investigations.

Investigations

The entire block of endometrium was serially sectioned. Histological examination showed proliferative phase endometrium. There was no evidence of tuberculosis. Ziehl-Nielson stained sections of the tissue showed no alcohol acid-fast bacilli.

Curetted uterine blood inoculated into Löwenstein's medium showed no growth after 6 weeks incubation.

A guinea-pig inoculated intramuscularly with curetted uterine blood was killed after 6 weeks. The tissues showed an indefinite reaction. Some of this material was subcultured into a second guinea-pig. On 14th May, 1955 guinea-pig number two was killed. It showed tuberculosis. Ziehl-Nielson stained smears of the tissue showed alcohol acid-fast bacilli.

Tuberculous endometritis was diagnosed.

Mrs. U. was admitted to hospital for treatment on 22nd May, 1955. No abnormalities were detected in the pelvis. Pulmonary and urinary investigations revealed no evidence of tuberculosis. She was given each day Streptomycin 1 g. intramuscularly and INAH 250 mg. in divided doses orally. After 3 months of combined therapy the patient was discharged in good health.

One month after completion of treatment Mrs. U. was well and gaining in weight. She was asked to come in for a curettage as she was too nervous to have an endobiopsy taken in the clinic.

She was admitted to hospital on 16th September, 1955. Examination under anaesthesia showed normal nulliparous genitalia, with the exception of the oviducts. Each was palpable, free and felt like a cord. The uterine cavity had decreased to 2¾ inches (7 cm.) in length. Menstrual endometrium totalling 1 inch (2·5 cm.) in diameter was curetted, it being the first day of her period. The specimen was sent for histological and bacteriological investigations.

Microscopic examination of serial sections of the endometrium showed no evidence of tuberculosis.

Endometrial suspension cultured on Löwenstein's medium showed no growth after 6-weeks incubation. Endometrial suspension inoculated intramuscularly into a guinea-pig produced no evidence of tuberculosis when the animal was killed 7 weeks later (8th November, 1955).

Mrs. U. was well and had no complaints when she was seen on 16th December, 1955. This was 4 months following cessation of therapy. Pelvic examination was entirely negative. The oviducts were not palpable. She was trying to become pregnant.

Pregnancy. The patient was admitted as an emergency case of hyperemesis gravidarum on 2nd October, 1956.

Her last menstrual period had begun 7 weeks previously. She responded to conservative treatment and was discharged 2 weeks later. Pelvic examination at this time showed an enlarging uterus and no adnexal abnormalities. Four weeks later a repeat examination confirmed a continuing uterine pregnancy. She remained in good health during the remainder of the pregnancy and attended the antenatal clinic regularly.

Labour. The forewaters were ruptured at 41½ weeks gestation (31st May, 1957) to induce labour. Uterine contractions developed the next day. She delivered a healthy infant after 20 hours of labour with the help of outlet forceps. The placenta complete with its appendages was sent for pathological and bacteriological investigations.

Puerperium. The mother remained apyrexial throughout the puerperium and her pelvic organs involuted normally. The female infant who weighed 8 pounds (3,632 g.) at birth was bottle fed as the mother failed to produce breast milk. The baby was vaccinated with B.C.G. The mother and her infant were discharged on the eleventh day post-partum.

Mrs. U. and her baby attended the postnatal clinic 10th July, 1957 (6 weeks post-partum). Both were in good health. Pelvic examination of the mother showed complete involution of her genitalia. The oviducts were not palpable. The baby had become immunized with B.C.G. At a follow-up visit a month later each continued in good health.

Treatment of Genital Tuberculosis

In view of the experience reported above it is helpful to review the recorded effect of various regimes of antimicrobial drugs given for female genital tuberculosis. A comment will follow on the therapy used in the two cases recorded here.

Five regimes of drug treatment have been employed in the treatment of pelvic tuberculosis (Table I). With a full course of Streptomycin and PAS, over 20 per cent of patients treated showed a recurrence of endometrial tuberculosis a year following cessation of therapy (Millar, 1954). Recently, Sutherland (1957a) reported a 12 per cent recurrence rate for similar therapy and for the same period of follow-up. He also emphasized that asymptomatic cases must be treated, for the disease progresses and can prove fatal. The relapse rate has been 10 per cent in cases treated with various drugs 2 years following completion of therapy, even in those cases showing a good early response (Stallworthy, 1952; Barns *et al.*, 1953; Rydén, 1953). INAH, Streptomycin and PAS combination appear to

TABLE I

Drug Treatment of Genital Tuberculosis

Drugs	Average Doses	Total Patients	Follow Up	Apparent Cure (per cent)	Authors
Streptomycin	1 g. daily for 3 months	184	4 to 12 months	52	Leroux and Guiheneuc, 1950 Zamorano, 1951 Rydén, 1953
Streptomycin and PAS	1 g. (Streptomycin) 12 g. (PAS) each for about 3 months	162	2 years	75 to 88	Sutherland, 1957a, b Millar, 1954 Stallworthy, 1957
Isoniazid (INAH) ..	150 mg. daily for 4 months	32	8 months	91	Barns *et al.*, 1953
INAH, Streptomycin and PAS	For 4 to 12 months or longer	29	On 18 patients 12 months	all but one	Barns *et al.*, 1953 Stallworthy, 1957 Snaith, 1957
INAH and PAS (Streptomycin if PAS not tolerated) ..	INAH 300 mg. plus 12 g. PAS every day for 1 year or longer. If PAS not tolerated 1 g. Streptomycin twice weekly.	Schaefer's regime (1955). No series yet reported; 4 months after treatment bacteriologic and microscopic examination of endometrial curettings and secretions done; and repeated every 3 months for several years. If negative he does tubal patency tests.			

have given the best results in the limited follow-up recorded in the literature. Further investigations have been in progress since May, 1953, under the Medical Research Council (Sutherland, 1957a) in which various combinations of anti-tuberculous drugs and different durations of treatment are being contrasted. The combinations of drugs and the duration of therapy which will achieve the maximum permanent cure rate have yet to be determined.

The complete treatment which gives permanent cure of genital tuberculosis has yet to be evolved. All authors agree that pelvic tuberculosis which does not respond to drug therapy requires surgical treatment. A difference of opinion exists regarding patients who are clinically cured. There are some who recommend surgery following successful endometrial cure, on the grounds that tubal caseous lesions may reactivate as they cannot be permanently cured (O'Driscoll, 1951; Knaus, 1954). In the post-reproductive age group, only time will show if this method is desirable. For women of pubertal or reproductive age most investigators favour conservative treatment with anti-tuberculous drugs, and a strict long-term follow-up (Schaefer, 1954; Sutherland, 1957a). This is the only form of therapy which gives hope for conception when genital tuberculosis has caused infertility.

In the cases reported here, the treatment given was Streptomycin 1 g. plus INAH 250 mg. each daily for 90 days to one patient; and Streptomycin 1 g. plus INAH 300 mg. daily for 120 days to the other patient. This combination was used because it was favoured at the time in the treatment of pulmonary tuberculosis. Each patient was delivered of a normal healthy baby within 2 years of the cessation of treatment (confinements were February, 1957 and June, 1957). The former patient is proceeding with her second pregnancy. So far in neither case has endometrial tuberculosis been found to have recurred. It is proposed to follow each case for 5 years. At present the question remains in these 2 cases (as in other cases reported elsewhere), whether endometrial cure means permanent or temporary oviductal cure in genital tuberculosis.

Genital Tuberculosis and Pregnancy

A consideration of the present knowledge of genital tuberculosis associated with infertility is pertinent in view of the accumulating evidence in the literature. Many patients with primary or secondary infertility due to pelvic tuberculosis wish to become pregnant. The incidence of pregnancy in untreated and treated genital tuberculosis is not common (Tables II and III). Since the introduction of anti-tuberculous drugs, an

Table II

Pregnancy and Genital Tuberculosis

Pregnancy following Untreated Proven Genital Tuberculosis		
Full-time pregnancies ..	10 cases	Yamaguchi (1951); Nevinny-Stickel (1952); Halbrecht (1955); Malkani and Rajani (1956); Gupta (1957); Fruhinsholz and Feuillade, 5 cases (1924)
Genital Tuberculosis Discovered After Termination of Pregnancy		
Full-time confinements ..	7 cases	Reviewed by Schaefer (1956)
Premature confinements ..	9 cases	
Abortions	12 cases	
Oviductal pregnancies ..	50 cases	

Table III

Pregnancy After Drug Therapy for Proven Genital Tuberculosis		
Full-time pregnancies ..	8 cases	Kullander (1952, bacteriology not done); Hallum and Thomas (1955); Halbrecht, 3 cases (1957); Norburn and Walker, 2 cases (1956); Sutherland (1957b)
Abortions	11 cases	Rabau (1952); Donaldson (1952); Stallworthy (1952); Barns *et al.* (1953); Halbrecht (1957); Bromberg and Rozin, 3 in same patient (1954)
Oviductal pregnancies ..	19 cases	Halbrecht (1957); Bromberg and Rozin, 1 in the same case as above (1954)

increasing number of conceptions is being reported following treated proven genital tuberculosis (Table III). In Halbrecht's (1957) series of 100 cases of genital tuberculosis treated with antimicrobial drugs 20 women conceived. Sixteen tubal pregnancies developed in 14 patients. Six intra-uterine pregnancies developed in the remaining 6 cases, of which 3 aborted and 3 went to term. Two of the 3 abortions later had tubal pregnancies. Halbrecht stresses that 80 per cent of the pregnancies developed in the tubes when proven tuberculous endometritis showed necrosis in the endometrium; whereas, only 45 per cent occurred in the oviducts when endometrial tubercles were not detected and only bacteriological proof was present. It would appear that oviductal pregnancies are common where conception follows proven genital tuberculosis treated with drugs.

Pathogenesis

The pathogenesis of genital tuberculosis has become clarified through the investigations of numerous workers. While primary inoculational tuberculosis of the vulva and cervix has been reported (Benjamin and Charnock, 1949; Schaefer, 1953) others deny its existence. Human tubercle bacillus is the infecting organism in the majority of cases (Jedberg, 1950; Haines, 1952; Sutherland, 1954; Millar, 1954). Clinical, macroscopic and microscopic evidence indicates that genital tuberculosis most frequently arises from a primary focus in the lung; which may have completely healed or shows radiologically evidence of inactivity (Jedberg, 1950; Liljedahl and Rydén, 1950). Post-primary haematogenous spread usually occurs within weeks (Auerbach, 1942; Choremis and Pantazis, 1952). Symptoms appear within one year in one-third of the cases and within 5 years in two-thirds of the cases (Schaefer, 1956). The outer portion of the oviducts are first involved. The lesion spreads via the submucosa to mucosa and serosa (Auerbach, 1942; Haines, 1951, 1952). The ovaries are involved by direct extension. The tubal mucosal tuberculosis spreads directly downwards to infect the adjacent cornual endometrium, progressing to involve the remainder of the endometrium (Jedberg, 1950).

Clinical Features

The clinical features of genital tuberculosis may be: none, infertility, menstrual disorders, pain, peritonitis, fistulae, or post-menopausal bleeding (Jedberg, 1950; Stallworthy, 1952, 1955; Sutherland, 1954, 1957a).

The majority of patients with tuberculous endometritis are without symptoms. The incidence of genital tuberculosis among infertility patients varies from 2 to 10 per cent with an average of 4 to 5 per cent (Halbrecht, 1946; O'Brien and Lawler, 1947; Jedberg, 1950; Liljedahl and Rydén, 1950; Sharman, 1952; Haines, 1952; Sutherland, 1954). In Britain, half the cases of genital tuberculosis are discovered during infertility investigations (Russell *et al.*, 1951; Stallworthy, 1952).

Menstruation is normal in half the cases. Excessive periods with an irregular cycle occur in almost half the cases; whereas, oligomenorrhoea with or without irregular bleeding is found in a small number; and amenorrhoea is rare (Sutherland, 1957b).

Pain although present in half the cases is not a prominent symptom. It is located in the hypogastrium with endometritis; in the iliac fossae with salpingitis or salpingo-oöphoritis; and over the sacrum with the exudative type of pelvic peritonitis which involves the utero-sacral ligaments.

Pelvic peritonitis may be primary with secondary infection of the internal genitalia, or it may complicate salpingitis and endometritis.

In the cases reported infertility was the major complaint. Each patient had menstrual disorders and complained of loss of weight. The latter would seem to be unusual. One had prolonged pelvic pain and palpable oviducts. In each the uterine cavity decreased in length following treatment (all the curettements and examinations at these times were done by the author).

Conclusions

(*A*) Living infants were delivered of two patients following treatment for proven genital tuberculosis associated with infertility. One of the patients is now proceeding in her second pregnancy.

(1) Anti-tuberculous drug therapy consisted of Streptomycin combined with INAH.

(2) Bacteriological proof was obtained from the endometrium in one case and from curetted blood in the other.

(3) Tubercles were not found in the endometrium in either case.

(4) The oviducts were palpable before treatment in one case, but were not felt following therapy.

(5) The elongated uterine cavity decreased to normal length following therapy in both cases.

(6) One patient developed genital tuberculosis following previous successful immunization with B.C.G.

(7) Insufficient time has elapsed for an assessment of the long-term results of treated genital tuberculosis followed by successful pregnancy in these two cases.

(*B*) From the evidence available in the literature, the position of genital tuberculosis in relation to infertility would seem to be, at present:

(1) Pregnancy has been reported in 20 per cent of women treated with drugs for genital tuberculosis.

(2) Of the pregnancies, 80 per cent developed in the oviducts where tuberculous necrosis was present in the endometrium; whereas, 45 per cent developed in the tubes, if tuberculous endometritis was diagnosed on bacteriological evidence alone. The total intra-uterine pregnancies remained the same in either group.

(3) Genital tuberculosis must now be considered as one of the important causes of infertility, tubal pregnancy and early abortion, in areas where tuberculosis is prevalent.

(4) Endometrium from the uterine cornua is most valuable in obtaining histological and/or bacteriological proof for a diagnosis of genital tuberculosis.

(5) The outlook for successful pregnancy remains poor, unless genital tuberculosis can be diagnosed and treated early.

(6) The most desirable therapy at present would seem to be Streptomycin plus INAH daily for 4 months in sanatorium.

(7) Treated and apparently cured tuberculous endometritis has recurred in 10 per cent of patients after 2 years. Follow-up should be for at least 5 years.

(8) Including the 2 cases recorded here, only 10 full-time pregnancies following antimicrobially treated proven genital tuberculosis have been reported. Insufficient time has elapsed to assess whether permanent cure and continued fertility have been achieved.

Acknowledgments

I wish to thank Dr. C. W. Taylor, Director of Pathology, the Birmingham and Midland Hospital for Women, for advice and criticism.

My thanks are also due to Mr. D. R. Cairns, Gynaecologist, Leicester General Hospital, for permission to publish; and to Dr. E. M. Stirk, Bacteriologist, Leicester General Hospital, for the histological and bacteriological investigations.

This is a shortened version of an article that received the Sheffield Clinical Research Prize.

References

Auerbach, O. (1942): *Surg. Gynec. Obstet.*, **75**, 712.
Barns, T., Smith, H. G. M., and Snaith, L. M. (1953): *Lancet*, **1**, 817.
Benjamin, F., and Charnock, F. (1949): *S. Afr. med. J.*, **23**, 667.
Bromberg, Y. M., and Rozin, S. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 121.
Choremis, C., and Pantazis, S. (1952): *Lancet*, **1**, 748.
Donaldson, I. (1952): *Brit. med. J.*, **2**, 128.
Fruhinsholz, A., and Feuillade, P. (1924): *Gynéc. Obstét.*, **10**, 305.
Gupta, S. (1957): *J. Obstet. Gynaec. India*, **7**, 181.
Haines, M. (1951): *Lancet*, **1**, 436.
Haines, M. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 721.
Halbrecht, I. (1946): *Schweiz. med. Wschr.*, **76**, 708.
Halbrecht, I. (1955): *Obstet. Gynec.*, **6**, 174.
Halbrecht, I. (1957): *Obstet. Gynec.*, **10**, 73.
Hallum, J. L., and Thomas, H. E. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 548.
Jedberg, H. (1950): *Acta obstet. gynec. scand.*, **31**, Suppl. 1.
Knaus, H. (1954): *Med. Klinik.*, **16**, 593.
Kullander, S. (1952): *Glasg. med. J.*, **33**, 395.

Leroux, M., and Guiheneuc, B. O. (1950): *Gynéc. Obstét.*, **49**, 479.
Liljedahl, S. O., and Rydén, A. B. U. (1950): *Acta obstet. gynec. scand.*, **30**, 359.
Malkani, P. K., and Rajani, C. K. (1956): *Fertil. Steril.*, **7**, 356.
Millar, W. J. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 372.
Nevinny-Stickel, H. (1952): *Geburtsh. u. Frauenheilk.*, **12**, 256.
Norburn, L. W., and Walker, A. H. C. (1956): *J. Obstet. Gynaec. Brit. Emp.*, **63**, 173.
O'Brien, J. R., and Lawler, M. K. (1947): *J. Obstet. Gynaec. Brit. Emp.*, **54**, 636.
O'Driscoll, D. T. (1951): *Lancet*, **2**, 476.
Rabau, I. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 743.
Russell, P. M. G., Jackson, M. H., and Midgley, R. L. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 712.
Rydén, A. B. U. (1953): *Acta obstet. gynec. scand.*, **32**, 368.
Schaefer, G. (1953): *Obstet. Gynec. Surv.*, **8**, 461.
Schaefer, G. (1954): *Amer. Rev. Tuberc.*, **70**, 1096.
Schaefer, G. (1955): *Amer. J. Obstet. Gynec.*, **69**, 1333.
Schaefer, G. (1956): *Tuberculosis in Obstetrics and Gynaecology*. Churchill, London.
Schaefer, G. (1957): *Amer. Rev. Tuberc.*, **75**, 501.
Sharman, A. (1952): *Fertil. Steril.*, **3**, 144.
Snaith, L. M. (1957): Personal communication to Schaefer, 1957.
Stallworthy, J. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 729.
Stallworthy, J. (1955): *in* Bourne, A. (ed.): *British Obstetrical and Gynaecological Practice. Gynaecology*. Heinemann, London. p. 681.
Stallworthy, J. (1957): Personal communication to Schaefer, 1957.
Sutherland, A. M. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 614.
Sutherland, A. M. (1957a): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 423.
Sutherland, A. M. (1957b): *Tubercle*, **38**, 46.
Yamaguchi, R. (1951): *World Obstet. Gynec.*, **3**, 954. (Abstr.: *Excerpta med. Amst.*, Sect. X, 1953, **6**, 18.)
Zamorano, L. B. (1951): *Boll. Soc. Chilena Obstet. Ginec.*, **16**, 17.

TUBAL PREGNANCY AFTER TREATMENT OF GENITAL TUBERCULOSIS

BY

W. GORDON MILLAR, M.B., Ch.B., M.R.C.O.G., R.N.V.R.

From the Royal Samaritan Hospital, Glasgow

WITH the earlier and more intensive treatment of tuberculous endometritis and salpingitis as practised today, it is likely that tubal damage will remain minimal and tubal patency will remain or be restored some time after treatment in a greater number of patients than before.

In a previous paper (Millar, 1954) describing the investigation and treatment of 36 cases of female genital tuberculosis, tubal patency was demonstrated in 5 patients 2 years after treatment. Two of these patients have subsequently become pregnant. One patient showed a positive pregnancy test after 6-weeks amenorrhoea but was admitted to another hospital with severe lower abdominal pain and slight vaginal bleeding. Tubal pregnancy was provisionally diagnosed as a small acutely tender mass was felt in the right adnexae. However, her condition improved after observation and laparotomy was not performed so there is no absolute confirmation of the presence of a tubal pregnancy.

The other patient was admitted to the Royal Samaritan Hospital recently with a right tubal pregnancy.

CASE REPORT

Mrs. J.H., aged 37 years (Case No. 30 in the published series) received treatment with streptomycin and P.A.S. in 1951 for tuberculous endometritis. The tuberculous lesion was discovered in 1947 after curettage for infertility and abdominal pain. Tubal inflation at that time showed tubal blockage.

In May, 1951, she was re-examined to confirm the tuberculous lesion before commencing treatment. The uterus was normal in size, position and mobility, the right tube and ovary felt normal, but the left tube was thickened and nodular. Tubal inflation again showed tubal blockage. Histological examinations confirmed the tuberculous endometritis. She received 90 days treatment with streptomycin and P.A.S.

Four subsequent examinations showed no evidence of tuberculous infection and in July, 1953, tubal inflation indicated tubal patency, the gas passing at a pressure of 70 mm. Hg. A previous inflation in June, 1952, showed apparent tubal blockage.

She was re-admitted to the Royal Samaritan Hospital on 2nd March, 1958. The last menstrual period occurred from 17th to 20th January, 1958, the cycle having been previously normal and regular. She had had abdominal pain for the last 12 days, localized to the right iliac fossa and coming in severe spasms with short periods of freedom from pain. A severe attack of pain was experienced on the night before admission to hospital, and remained constant. There was no nausea, vomiting nor vaginal bleeding. Bowel function and appetite had remained normal but slight frequency of micturition had occurred in the last four weeks.

On vaginal examination, the uterus was anteverted without significant enlargement. There was acute tenderness and a small mass in the right adnexae.

On 3rd March, 1958, examination under anaesthesia confirmed the soft right adnexal mass. At laparotomy immediately afterwards free blood was present in the peritoneal cavity. A chorionic sac was protruding from the fimbriated end of the right tube with free bleeding from the tube. Tubal abortion was about to occur. A right salpingectomy was performed. The left tube was noted to be slightly thickened and the fimbriated end was inverted but patent. A foetus of approximately 5-weeks maturity was recovered from the sac.

On histological examination of serial sections of the right tube, there was no sign of tuberculosis but the tubal wall was considerably thickened near the implantation site. The implantation site showed normal chorionic villi, decidual reaction and increased vascularity.

The post-operative recovery was uneventful and she was allowed home on the 15th March, 1958.

Discussion

Sharman (1952) found tubal patency in one-third of 149 patients in whom tuberculous endometritis had been discovered during investigation for infertility. This is a higher incidence of tubal patency in such cases than that generally experienced, but is explained by the fact that all the patients had no complaints other than infertility. In unselected cases of genital tuberculosis the incidence of tubal patency is much lower, being approximately 13 per cent (Millar, 1954).

Nevertheless, it is surprising that there have been so few recorded instances of tubal gestation in association with active tuberculous salpingitis. Davin-Power, O'Dwyer and Leslie (1955) in reporting one such case could only find 2 other recorded instances in the British literature and 52 cases in the World literature.

There are 3 possible explanations for the low incidence of tubal pregnancy in patients with tuberculous endometritis who show tubal patency:

(1) We may be wrong in assuming the presence of tuberculous salpingitis when tuberculous endometritis is discovered in association with tubal patency.

(2) The presence of an active tuberculous infection may itself be a barrier to successful nidation and imbedding of the ovum, either in the tubes or in the uterus.

(3) Many patients complaining of infertility would be infertile whether tuberculosis was present or not.

Since reporting the original series of 36 cases, I have treated a further 46 cases of tuberculous endometritis. The period of surveillance is not completed, but, so far, 6 patients have shown tubal patency following treatment. One patient became pregnant during treatment and is now 38-weeks pregnant and progressing normally.

In the patients with tubal patency, the kymographic tracing often shows very poor tubal motility and passage of the gas at higher pressures, suggesting some degree of tubal stenosis. Theoretically, the risk of tubal pregnancy in these patients is much greater. Recanalization of slightly damaged tubes is a distinct possibility. Three patients in the previous series, who had apparent tubal blockage after repeated insufflations at a pressure of 250 mm. Hg before treatment, showed tubal patency 2 or more years after treatment. The present case report was one of these patients and 2 years after her treatment gas failed to pass, but insufflation 3 years after treatment showed passage of gas at a pressure of 70 mm. Hg, but with no tubal peristalsis. Tubal stenosis was probably present and was confirmed by microscopic examination of the tube. It appears to be the likely cause of the tubal pregnancy in this case.

Time will tell how great the hazard of pregnancy may be in similar cases.

Summary

(1) A case of tubal pregnancy occurring 7 years after the treatment of tuberculous endometritis and salpingitis is reported.

(2) In slightly damaged tubes, recanalization seems likely after a long period.

(3) An increased incidence of tubal stenosis following treatment of genital tuberculosis may predispose to tubal pregnancy.

Addendum

Since the above paper was written, another patient in the original series (Case No. 9) was admitted to the Samaritan Hospital with a ruptured tubal pregnancy 8 years after treatment of tuberculosis.

Tuberculous endometritis was treated in 1950 with streptomycin and P.A.S. Tubal inflation at that time showed apparent tubal blockage but no adnexal masses were felt. Routine examinations until 1954 showed no evidence of tuberculosis but tubal inflation in 1953 was again unsuccessful.

On 6th May, 1958, she was admitted with a history of 5-weeks amenorrhoea, severe right lower abdominal pain, but no vaginal bleeding. Tenderness on vaginal examination was very acute. Laparotomy confirmed the presence of a right-sided ruptured tubal pregnancy with free blood in the peritoneal cavity. Salpingectomy was followed by an uneventful recovery. Histological examination of the tube confirmed the pregnancy and, although there were no signs of tuberculous infection, the tubal plicae were adherent in some areas.

References

Davin-Power, M. M., O'Dwyer, J. P., and Leslie, D. A. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 957.

Millar, W. G. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 372.

Sharman, A. (1952) *J. Obstet. Gynaec. Brit. Emp.*, **59**, 742.

INFANT MORTALITY IN NORTHERN NIGERIA, WITH ESPECIAL REFERENCE TO THE BIROM TRIBE

BY

R. F. R. GARDNER, L.R.C.P.&S.(Edin.), L.R.F.P.S.

AND

ELIZABETH S. GARDNER, L.R.C.P.&S.(Edin.), L.R.F.P.S.

Medical Officers

Sudan United Mission Hospital, Vom, Northern Nigeria

INTRODUCTION

THE apalling infant mortality in tropical Africa has long been recognized, but has been little studied. Jelliffe (1952) writes: "The variety and vagueness of estimates of infant mortality in different parts of Africa was well shown at the 1st International Conference on the African Child (Sharpe, 1931) when figures ranging from 100 to 500, and even up to 820, were given. It is my guess that the infant mortality is generally in the region of from 300 to 500 in most of Africa."

A few scattered figures have been published for various parts of the continent. Worthington (1938) quotes a Belgian Government census report from Ruanda Urundi in 1935, giving an infant mortality rate of 100 per thousand live births among the most primitive class, and also quotes a French census report of 200–250 deaths per thousand, before the age of 3 years, in the Cameroons. Janssens (1952), working in the Belgian Congo, found an infant mortality rate fluctuating between 200–400 per thousand in the years 1937–48, while Kivits (1951) in the same country reported among children delivered in hospital an infant mortality rate of 132 per thousand live-births. From her clinics among the Anyanja and Ayao peoples of Nyasaland, Dabb (1952) reports figures representing a death rate of 239 per thousand live births, before the age of 12 months; while in Tanganyika during the period 1941–52 Nhonoli (1954) found a rate of 308 per thousand live births among his own people, the Nyamwezi. By recent unpublished surveys Merriweather (1957) estimates the rate among the Bakwena of Bechuanaland to be 170 per thousand live births, and McCulloch (1957) 238 per thousand live births among the more educated sections of the Lala people of Rhodesia.

For West Africa Maass (1929) working up-country in Liberia found a death-rate of 317 per thousand under the age of two years, while Jelliffe (1952) quotes figures for coastal cities in 1946 of 110 in Accra, 153·8 in Bathurst and 208 in Freetown. Gamble (1952) investigated four Mandinka villages in a rural area of the Gambia protectorate, finding a mean infant mortality rate of 420; he also quotes Harding (1948) as finding a rate of 417 ($\pm$48) in an unsophisticated community in Sierra Leone. Two recent investigations, not so far reported in the medical literature, yield figures as follows: Rose (1956) in the course of a Kwashiorkor survey in the South-East Province of Sierra Leone estimated the infant mortality at 627 per thousand. As part of the vast demographical survey of parts of French Guinea the mortality rate in the first year of life was found to be 226 (in rural areas) and 142 (in urban areas) per thousand live births (Guinée, 1956).

Here in Nigeria the official report for 1953 (Nigeria, 1955) states "There are no accurate vital statistics except for Lagos". There, by 1956, the Infant Mortality Rate had fallen to 78·1 per thousand live births (Lagos, 1957).

Present Position in Northern Nigeria

For the vast Northern Region, with a population of some 17 millions, very little work has been recorded. The few figures which have been collected, in many cases by anthropologists or administrators, exist for the most part only in manuscript. The only reference traced in the medical literature is to a nutritional survey of the city of Katsina by McCullough (1929–30) during the course of which he found an infant death-rate of 412 per thousand.

In an attempt to provide a broad picture of present-day conditions in this region, many of the leading mission hospitals have co-operated by collecting data. These, together with figures collected by government medical teams in the last few years, but not hitherto published, are shown in Table I.

Table I

Child Mortality Rates of Indigenous Peoples in Various Areas of Northern Nigeria

Section A: Figures Collected in 1957 from Mission Hospitals in Connexion with this Study
Section B: Figures Collected by Government Medical Field Units since 1950, but not Previously Published.

Source	Place and Province	Tribes	Women	Live Births	Deaths	Deaths Per Thousand	Notes
Section A: Mission Hospital Data:							
Gray, H. H.	Takum, Benue	Kutev Jukun Tiv Hausa	334	913	280	306	Antenatal clinic histories
du Toit, Maria	Mkar, Benue	Tiv	500	1,501	303	202	Antenatal clinic histories
Olewiler, D. B.	Bambur, Adamawa	Bambur	54	322	178	552	Non-pregnant women questioned at home
Erb, Jean	Tungan-Magajiya, Niger	Dukawas Dakkakari	40	218	180	825	Antenatal clinic
		Fulani Hausa	40	167	74	440	Non-pregnant women questioned in hospital
Ware, Winifred	Kabwir, Plateau	Angas	100	489	320	634	Antenatal clinic
Campion, G. F.	Egbe, Ilorin	Igbomina	55	258	137	531	Antenatal clinic histories
		Yagba	91	288	63	218	
Section B: Field Medical Unit Mass Morbidity Survey Figures:							
Haworth, J.	Meringa, Bornu	Barbur	85	301	135	448	Before weaning
	Askira, Bornu	Marghi Higgi	212	823	181	220	Before weaning
	Sakwa, Bornu	Bura	328	1,596	677	422	Before weaning
	Biu, Bornu	—	—	77	40 Infant mortality	519*	Within 12 months*
	Konduga, Bornu	Kanuri	—	39	9 Neonatal	231*	Within 30 days*
Horn, D. W.	Kalgo, Sokoto	Hausa	1,177	—	—	288	Before weaning

* Direct observation, see text.

The astonishing inconsistency in the obstetrical histories given by some African women is a source of possible error in almost all African series. Of especial interest, therefore, are some figures collected by Haworth (1957) and annotated "Direct observation" in part B of the Table. During the course of his surveys the names of women observed to be pregnant (5 months or more) were noted, and these were followed up at 6-monthly intervals. From such observations a more accurate figure can be arrived at than is usually possible in primitive conditions.

The wide range of mortality figures is probably due, in part, to the selection of women for questioning. In all cases southern immigrants, mostly wives of traders and clerks, have been excluded from the investigations. In presenting figures for Tungan-Magajiya, Erb comments that apart from such southerners the only women so far attending the antenatal clinic are those suffering from "wabi", a Hausa word descriptive of the mother who constantly suffers the loss of young children. When, therefore, she questioned a similar number of women attending hospital for non-obstetrical complaints, a completely different, and much smaller death-rate was obtained.

It is the purpose of this paper, therefore, to present in some detail figures from one tribe where, medical work having been established for more than 30 years, all sections of the community willingly attend for antenatal care. In view of this, and the close correspondence which will be shown between series from two parts of the tribe, it is felt that these figures present a reasonably accurate picture of conditions as they obtained among the Birom in 1957.

Tribal Background

The Birom (or Bi Rom), are a people believed to be of Hamitic-Jukun descent, speaking a semi-Bantu language and now inhabiting some 1,020 square miles in the Jos Division of Plateau Province in Northern Nigeria (Lat. 10° N., Long. 9° E.). Their tribal area is open rolling countryside at an elevation of about 4,000 feet above sea level, with rocky outcrops rising to 6,000 feet. The Birom, estimated in 1945 as 55,700 strong, but now much more numerous, live in villages consisting of clusters of huts surrounded by stockades of *Euphorbia candelabrum* (Forde, 1946; Davies, 1949; Buchanan and Pugh, 1955).

Polygamy is practised, although for economic reasons it is uncommon for a man to have more than two wives. In addition, there is a custom, unknown in the surrounding tribes, which amounts to polyandry. This is an arrangement of "secondary marriages" by which a man purchases the right of access to a neighbour's wife over prolonged periods, usually a year at a time. Payment for the privilege may be in kind, in cash, or by working on her husband's farm. The woman herself is given an occasional gift, perhaps of meat. Any children born of such a liaison are recognized as those of the legal husband, and there is no discrimination against them.

Sterility is very uncommon and an average of 10 pregnancies is said to occur in a "completed marriage" (Barnden, 1957). Davies (1949) states that "the infant mortality rate of the Birom is not known but is probably as much as 40 per cent. The number who die before reaching maturity is better known and is approximately 60 per cent." He also quotes two series of figures to which he had access in administrative records. One report was by Black who questioned 82 Birom women who reported that 47 per cent of their children survived and one was by Pitcairn who, dealing with an older age-group of 247 women, found that 40 per cent of their offspring had survived. No mortality rates are, however, mentioned.

Present Investigation

During the twenty months from October, 1955, to June, 1957, all patients attending the antenatal clinic at this hospital have had details of their previous pregnancies recorded for analysis. Those referring to parous Birom women form the basis of this study; 1,383 women gave a history of having previously given birth to 4,306 live babies. Of these babies, by the time of the coming of the mother to the clinic, 2,114 had died, giving an overall mortality of 490·9 per thousand live births. This constitutes

the Vom series which will be referred to later; most of the women come from Vom (Vwang), and nearby villages of the Western section of the tribe.

This mission, also, has a small maternity unit at Forum, in the eastern section of the tribe. The Forum records for nine months, August, 1956, to April, 1957, involving 580 women, were also examined. They show 957 deaths out of 1,955 live births. The two series have been combined (Table II) to give a picture of the tribe as a whole. The mortality rate is unchanged at a mean of 490·5 per thousand live births.

TABLE II

Relationship Between Parity of Mothers and Mortality of Birom Children

Parity	Number of Women	Total Live Births	Total Deaths	Mortality per Thousand Live Births
1	466	437	193	441
2	420	800	326	407
3	330	953	432	453
4	265	1,032	478	463
5	174	854	413	462
6	115	672	360	535
7	81	550	304	544
8	51	393	227	578
9	40	352	201	596
Over 9	21	218	137	628
Totals ..	1,963	6,261	3,071	Mean: 490·5

AGE OF DEATH

Figures of African child mortality are not strictly comparable with European rates, nor with each other. Except in the largest towns, there is no system of birth certification, and there is no means of judging the age of the child with accuracy. In the first Clinical Report from the obstetrical unit at Ibadan attention is drawn to the fact that accurate record-keeping is hindered as only members of the small literate minority know the year of their birth or the month of their last menstrual period (Lawson and Lister, 1955).

Horn (1957) has suggested that it is only possible to calculate accurately "suckling" and "puberty" mortality rates, which may be taken as deaths under 2 years, and under 15 years, respectively, as working approximations. The primitive African has very little means of noting the passage of time, and indeed has an entirely different concept of it from the European (Fueter, 1956). So much is this so that, despite frequent promptings, the African midwives taking histories omitted, in most cases, to ask the age at death. It is interesting to find that Dabb (1952) faced the same problems in her Nyasaland series. At Vom, however, in the cases of 551 children, this information is available. These cases were quite unselected and are scattered indiscriminately through the whole Vom series, forming a true random sample. They are presented, recorded separately by birth rank in Figure 1. It was found that 40 per

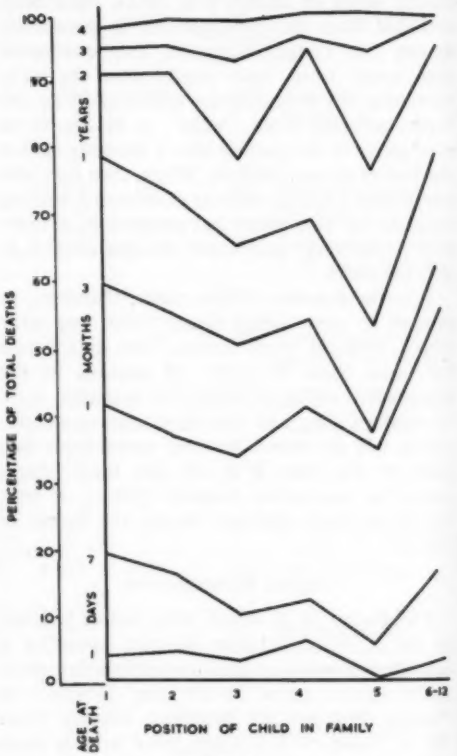


FIG. 1

Cumulative percentages of total deaths, in relation to age at death, and position of child in family.

cent of deaths occurred in the first month, 74 per cent under the age of 1 year, and 91 per cent under the age of 2 years. In less than 1·1 per cent of cases was the child over 3 years of age at death.

If this sample is true of the whole series it would represent a neonatal mortality rate (i.e., death within the first month of life) of 195 per thousand live births, and an infant mortality rate (i.e., death within the first year) of 358 per thousand live births.

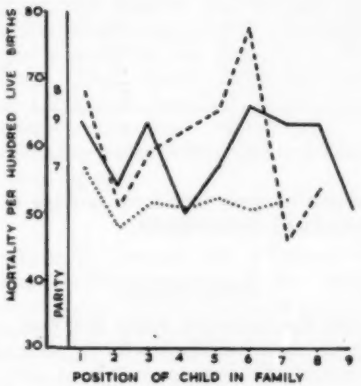


FIG. 2

Mortality expectancy by birth rank, families of 7–9 children.

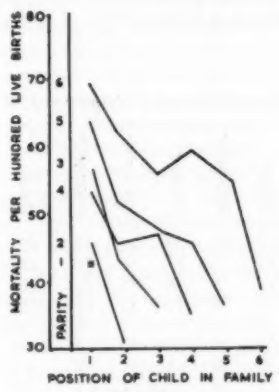


FIG. 3

Mortality expectancy by birth rank, families of 1–6 children.

MORTALITY EXPECTANCY IN RELATION TO BIRTH RANK

An examination was made of the Vom series for mortality rates in relation to birth rank. The results are presented in Figures 2 and 3. In Figure 2, relating to women who have borne 7, 8 or 9 children, no particular pattern is obvious; but in Figure 3, relating to those with smaller families at the time of the study, a very clear pattern emerges, the expectancy of survival for each child being more favourable than for its older sibling. Gamble (1952) describes a similar pattern in the Mandinka people of the Gambia Protectorate.

CAUSES OF DEATH

The mothers were quite unable, in most cases, to give any idea of why the child died, although a few reported a bout of diarrhoea, cough, or convulsion as having occurred just before death. An examination was made, therefore, of the hospital case-papers of all Birom children under the age of 3 years old, admitted to this hospital during the year 1956. The local people are not yet willing to be separated from their children and so children are admitted to our Birom accommodation along with their mothers who take care of them. In view of this, only when a child is obviously seriously ill will the parents agree to admission, except when they come from a considerable distance, and so a minority of the children seen at this hospital are treated as in-patients.

During the year under review, 53 Birom children under the age of 3 died in hospital. Details are shown in Table III.

An examination of this reveals that, as 68 per cent of all deaths took place within 24 hours of admission to hospital, and a further 11 per cent within the second 24 hours, many of the children were moribund on admission. In the case of uncomplicated respiratory infections, which are by far the commonest diseases of childhood in this area, 94 per cent of the deaths occurred within a few hours of admission. In this series it seems likely, therefore, that many deaths, being preventable, were due to delay in the parents seeking medical advice.

TABLE III

Cause of Deaths in Hospital of Birom Babies Under Age of 3 Years

Diagnosis	Number of Cases			Time of Death After Admission		
	Total	With Convulsions	Without Convulsions	0–24 Hours	24–48 Hours	More Than 48 Hours
1. Infections of respiratory tract:						
(*a*) Uncomplicated ..	18	5	13	17	0	1
(*b*) With malaria	6	2	4	6	0	0
(*c*) With dysentery ..	1	0	1	0	0	1
(*d*) With cellulitis ..	1	0	1	0	0	1
2. Dysentery	8	1	7	4	1	3
3. Malaria	6	4	2	2	3	1
4. Malnutrition and anaemia	3	0	3	2	0	1
5. Waterlogged from "shok"	3	0	3	3	0	0
6. Other conditions	7	3	4	2	2	3
	53	15	38	36	6	11

To get a realistic picture of the disease pattern in the district all admissions of Birom children under the age of 3 years, during the year under review, are tabulated in Table IV.

Gelfand (1947) has commented that, whilst European medical students are taught, as a rule, not to diagnose more than one disease, this instruction must be forgotten when dealing with the African. It is not surprising, therefore, to find 1,304 diagnoses in the 834 cases enumerated. The monthly variation in admissions is probably not so much due to a true change in the incidence of disease, as to the readiness of the parents to spare time from farming to stay in hospital with their children.

BIRTH WEIGHT

During the period in which the Vom series was being collected 527 live births occurred in this hospital. The average weight at birth was 6 pounds ¼ ounce (2,728·7 g.). This compares with a Lagos figure of 6 pounds 13 ounces (3,090·2 g.) (Whitbourne, 1930), and an Ibadan one of 6 pounds 5 ounces (2,863·4 g.) (Jelliffe, 1952). Geber and Dean (1957) of Makerere have

TABLE IV

Disease Pattern Among Birom Children Under the Age of 3 Years, Admitted to Hospital in 1956

	January	February	March	April	May	June	July	August	September	October	November	December	Totals	Percentage of Total Diagnoses
Respiratory infections ..	25	39	34	37	43	49	45	32	15	40	33	32	424	32·4
Dysentery	13	11	23	27	32	27	24	13	7	27	30	20	254	19·5
Malaria	2	8	19	18	35	26	23	16	8	39	47	22	263	20·2
Superficial infections ..	8	5	2	5	8	5	9	2	8	11	13	11	87	6·7
Conjunctivitis	1	2	1	2	2	6	3	3	4	7	3	1	35	2·7
Malnutrition and/or anaemia	2	3	6	5	11	5	6	1	3	17	10	5	74	5·7
Meningitis	2	1	0	1	2	0	0	0	0	1	2	0	9	0·7
Injuries	1	0	3	1	2	0	1	3	0	1	1	1	14	1·1
Convulsions	4	3	2	2	7	5	5	4	1	22	13	6	74	5·7
Others	1	9	6	6	7	3	4	4	6	12	7	5	70	5·4
Patients admitted	49	61	70	71	93	80	81	55	39	91	85	59	834	

drawn attention to the impossibility of knowing the length of gestation in African women because of their ignorance of the date of their last menstrual period. Because of this, it is impossible to be sure that in this, or any African series, only full-term babies have been included.

Sex Ratio

In view of the finding of Trolli (1934), quoted by Worthington (1938), that among the Bakongo people there was a predominance of female births, it was decided to investigate the sex ratio. To obtain a sufficiently large series the hospital records for the past five years were examined. They yielded 1,956 live births of which 1,033 were male and 923 were female. This represents a ratio of 108 male to 100 female births, which is very similar to the usual European figures.

Discussion

Children are wanted and welcomed by the African—for their own sake, as extra hands for the farm, and as an insurance against an old age of poverty. Carothers (1953) has summed up the position thus: "The mother is devoted to her baby, carries him wherever she goes in close contact to herself, handles him with confidence, panders to all his whims, and feeds him on demand. He lives in a smooth, warm, rhythmic world, soothed by her voice and crooned to sleep in her arms. He is indulged to a fault, and his excretory activities are unrestrained."

The Birom space their familes with care. Not until her youngest baby can walk by itself does a woman permit the resumption of coitus. This particular duration of abstinence must be common among primitive peoples: Van der Hoeven (1956b) noted it in New Guinea, and Krzywichi (1934) found it to be the practice in 10 of the 62 African men he questioned. Nevertheless the fact does not seem to have been widely recognized by Western observers. A birth occurring less than two years after that of a previous surviving child is regarded as a disgrace among the Birom, as among many African tribes (Trowell, Davies and Dean, 1954). In some parts of the continent an infant which deprives its predecessor of its full birthright of breast feeding is given a name which carries a stigma for the mother for conceiving again too soon (Platt, 1954).

André and Holemans (1955) found prematurity and congenital debility (with birth weight as the criterion of these) to be the major cause of perinatal mortality in their Congo babies. Van der Hoeven (1956a), however, has suggested that tropical babies with a birth weight of less than 2,500 g. should not necessarily be thought of as premature, as their weight technically demands, but as "unripe". On the other hand, as was pointed out in East Africa by Scotland (Mulago, 1954), the average occipito-frontal circumference of an African baby weighing 5 pounds (2,268 g.) equals that of a 6½ pounds (2,950 g.) British baby. Such small African babies, therefore, have mature heads. Woodruff (1954) feels that low birth weight and high neonatal and infantile mortality are often the result of deficiency of foetal building materials and particularly of protein.

No preparation is made for the arrival of the child and it is by no means infrequent for a woman to go to work in the field and to return with a baby which has been born by the roadside. The mother stays at home to nurse the child for the first two months, but then must return to farm work, as the folk live so near to starvation level that no able hand can be spared from the soil. As a relic of the slave-raiding days Birom villages are normally situated in defensible areas in the hills, and as a result there is often a distance (6–7 miles in the case of Vom) between hut and farm. It will be seen, therefore, that the mother is often away from home for a continuous period of from 7 to 8 hours. The infant is left at home in the care of the paternal grandmother, who feeds it with water, or occasionally, after the age of 6 months, with a little gruel. The baby is laid down flat and fluid is poured from the cupped unwashed hands, usually until its abdominal wall is taut and bulging. This custom (for which the Birom word is, appropriately enough, "Shok") is very similar to the Yoruba custom of "pap" described by Jelliffe (1952). This procedure may result in serious consequences, such as aspiration pneumonia, as has also been pointed out by Bruce-Chwatt (1952) and Horn (Lagos, 1957).

Water is drawn from springs or from the stream which flows through the village. Various parts of the common ground are set aside for defaecation, and as there is no other system of sanitation, the streams are heavily contaminated, especially at the beginning of the wet season, and dysentery is rife.

There are two cold seasons in the year, one in December during the dry season, and the other in June–September during the rains. At night the temperature may fall to 45° F. (7·2° C.) and the family sleep huddled up with a low fire burning. It is not to be wondered at that, as the children wear nothing at all (and their mothers only a bunch of leaves) respiratory diseases head both morbidity and mortality tables. Drawing attention to the cold nights which may occur even in the tropics, Van der Hoeven (1956a) included thermolability in his list of the special hazards which the "unripe" child has to face. The prime importance of respiratory diseases is the common finding throughout Africa. They were found to be the cause of death in 42·5 per cent of 830 autopsies on African infants under the age of 1 year, at Lagos in the period 1935–50 (Bruce-Chwatt, 1952), while Janssens (1952), in the course of 1,873 post-mortem examinations of infants in the Belgian Congo, found that 974 deaths were due to respiratory diseases (in 835 cases, broncho-pneumonia, with or without complications). Kivits (1951) found that of his hospital admissions 35 per cent were due to broncho-pneumonia or whooping cough. Despite the fact that Jelliffe (1957) feels that pertussis is an important cause of childhood morbidity in the tropics, and is possibly increasing in incidence, it played only a minor role at Vom in 1956, contributing only 34 to the 424 cases of respiratory diseases admitted.

Whitbourne (1930) lists convulsions as the cause of death in 24 per cent of his cases. It is difficult to estimate the true importance of convulsions in our series, but their adverse effect on the prognosis is seen by the fact that whilst only 6 per cent of our admissions died, the death rate rose to 20 per cent among the group with convulsions.

Children rarely eat meat which is considered a luxury and is available only on special occasions. The milk of animals is commonly believed to be unsuitable for human consumption. Their normal dietary consists almost solely of maternal milk with the addition of a gruel, and still later, a porridge. The staple grain from which the gruel and porridge are produced is Acca (*Digitaria exilis*) which gives a poor yield but is fortunately rich in protein. Severe anaemias, and gross degrees of kwashiorkor and other forms of malnutrition are infrequently encountered. This is in complete contrast to the picture seen at Ibadan and elsewhere in the southern areas of the country (Collis, 1957).

Bruce-Chwatt (1952) and McGregor and his co-workers (1956) have discussed the problem of malarial infections in West African infants. At the time of this study facilities for routine blood examination were not available and therefore no detailed study of the influence of malaria was made. In those children from whom blood smears have been taken more recently, heavy infections of *Plasmodium falciparum* have been found.

At birth it is the Birom custom to cut the umbilical cord with a knife (in the case of a boy) or a strong piece of grass (for a girl). Despite this, umbilical infections are rare, and only one case was seen in 1956; in this, however, there was a fatal outcome. Davies (1949) has vividly described the level of hygiene thus: "Children are always filthy. They play in the sandy open spaces in the village so that their bodies are always grimy and they have food smeared over their faces and urine lines running down their dust covered legs. Washing of children is not popular as it is said to cause diarrhoea if done too often." Scabies was found to be widespread and accounted for more than half of the superficial infections listed in Table IV.

Burns, which made up most of the injuries seen, are due to the child being left in the care of some little sister who is quite unfitted for the responsibility and permits the crawling infant to fall into the fire. Carothers (1953) has pointed out how commonly this occurs all over Africa.

Meningitis is a disease of the dry season (October to April) in Northern Nigeria and in some years there are widespread epidemics.

In fact, Horn (1951), who believes it to be the greatest scourge of all epidemics in Nigeria, reported an epidemic causing at least 93,000 known cases in 1949/50, with an attack rate in Plateau Province of 28 per thousand of the population. Only a few cases were seen at Vom, however, in 1956. Similarly, measles, of which there was an epidemic in 1955, and small-pox which struck heavily in 1957, were not seen in the year under discussion.

Conclusions

It will be observed from Figure 3 that the mortality rate has tended to drop over the years. As Birom women normally give birth about every 2½ years, this represents a period of about 15 years, from 1939 to 1954. The mortality rates range from 690 per thousand in the first group of 1939 to 370 per thousand in the last group about 1954.

Various factors have played their part in this improvement. With increasing demands for labour in the tin mines, Birom men have found employment with a consequent improvement in family economy. Education is slowly spreading with the new schools and increased church membership. and this has its influence in elementary hygiene. With the build up of confidence of the local population there has been a greater willingness to use the facilities of antenatal clinic and hospital.

Despite this improvement, however, conditions are still appalling by even the lowest standards of Western medicine, while the need and opportunities are endless. Platt (1954) has reiterated his view on the importance of making maternity and child welfare work the starting point of a campaign against ill-health in backward countries. In the words of a recent editorial comment (*British Medical Journal*, 1956) "No doctor need bemoan the uniformity of the Welfare State or the drabness of work under the National Health Service until he has failed to find employment in Nigeria".

Summary

The variety and vagueness of infant mortality rates in Africa is commented upon. Figures from the literature and several hitherto unpublished series, are reviewed.

A series of new figures, covering most of the Provinces of Northern Nigeria, and ranging from 202 to 825 deaths per thousand live births, is presented.

A particular tribe, the Birom, are described and the fate of 6,261 babies born to 1,963 Birom women discussed. In this series, the Neonatal Mortality rate was 195 and the Infant Mortality rate 358 per thousand live births; while the overall child mortality rate was 490 per thousand.

The causes of morbidity in 834 admissions, and of death in 53 cases in Birom children under the age of 3 years, are discussed. Respiratory infections, dysenteries and malaria, in that order, are the principal conditions seen.

Attention is drawn to the steady fall, year by year, in infant mortality and possible causative factors are briefly mentioned.

Acknowledgments

We gratefully acknowledge the co-operation of the following colleagues who collected data for this study: Drs. H. H. Gray and D. B. Olewiler, Sisters G. Stokes, C. Norheim and W. Ware of the Sudan United Mission, Dr. G. F. Campion of the Sudan Interior Mission, Dr. J. Erb of the United Missionary Society, Dr. M. Du Toit, *O.B.E.*, of the Dutch Reformed Church Mission, Dr. A. Merriweather of the United Free Church and Dr. J. E. McCulloch of the Church of Scotland.

We also wish to thank Professor Collis of the Paediatric Department and Dr. Lawson of the Obstetric Department, University College Hospital, Ibadan, for their help; and Dr. D. W. Horn, Federal Medical Statistician, Dr. J. Haworth of the Northern Regional Medical Headquarters; and Dr. J. R. Rose of the Methodist Missionary Society for placing their figures at our disposal, and M. Eyquem, Chef du Service de la Statistique Générale et de la Mécanographie de la Guinée, for providing us with data.

We record our appreciation of the constant encouragement, advice and assistance given by Dr. J. I. Taylor, Ph.D., Federal Director of Veterinary Research, Vom.

References

André, J., and Holemans, K. (1955): *Ann. Soc. belg. Méd. trop.*, **35**, 661.

Barnden, P. W. (1957): Personal communication.

British Medical Journal (1956): *Brit. med. J.*, **1**, 390.

Bruce-Chwatt, L. J. (1952): *Ann. trop. Med. Parasit.*, **46**, 173.

Buchanan, K. M., and Pugh, J. C. (1955): *The Land and People of Nigeria*. English Universities Press, London.

Carothers, J. C. (1953): *The African Mind in Health and Disease. A Study in Ethnopsychiatry*. W.H.O. Monograph Series, No. 17. World Health Organization, Geneva.

Collis, W. R. F. (1957): Personal communication.

Dabb, R. G. (1952): *E. Afr. med. J.*, **29**, 439.

Davies, J. G. (1949): *The Bi Rom*. Unpublished MS. in the Library of the Administrative Office, Jos.

Forde, D. (1946): *Native Economies of Nigeria*, ed. M. Perham. Faber and Faber, London, for Nuffield College.

Fueter, P. D. (1956): *Int. Rev. Missions*, **45**, 377.

Gamble, D. P. (1952): *J. trop. Med. Hyg.*, **55**, 145.

Geber, M., and Dean, R. F. A. (1957): *Lancet*, **1**, 1216.

Gelfand, M. (1947): *The Sick African, A Clinical Study*. 2nd edition. Stewart Publishing Co., Cape Town.

Guinée (1956): *Enquête démographique de Guinée, 1954–55. Resultats Provisoires*, Fasc. 2. Haut Commissariat de l'Afrique Occidentale Française, Paris.

Harding, R. D. (1948): *Population Stud.*, **2**, 373.

Haworth, J. (1957): Personal communication.

Horn, D. W. (1951): *J.R. sanit. Inst.*, **71**, 573.

Horn, D. W. (1957): Personal communication.

Janssens, P. G. (1952): *Mem. Inst. roy. Colon. belg., Sect. Sci., Natur. Méd.*, **20**, 134.

Jelliffe, D. B. (1952): *Trans. R. Soc. trop. Med. Hyg.*, **46**, 13.

Jelliffe, D. B. (1957): *W. Afr. med. J.*, **6**, 72.

Kivits, M. (1951): *Mem. Inst. roy. Colon. belg., Sect. Sci., Natur. Méd.*, **19**, 33.

Krzywichi, L. (1954): *Primitive Society and Its Vital Statistics*. Macmillan, London. (Quoted by Platt, 1954.)

Lagos (1957): *Annual Report of the Medical Services of the Federal Territory of Lagos for the year 1956*. Federal Government Printer, Lagos.

Lawson, J. B., and Lister, U. G. (1955): *Clinical Report on the Department of Obstetrics, University College, Ibadan*.

Maass, E. W. H. (1929): *W. Afr. med. J.*, **3**, 34.

McCulloch, J. E. (1957): Personal communication.

McCullough, W. E. (1929–30): *W. Afr. med. J.*, **4**, 8, 36, 62.

McGregor, I. A., Gillies, H. M., Walters, J. H., Davies, A. H., and Pearson, F. A. (1956): *Brit. med. J.*, **2**, 686.

Merriweather, A. (1957): Personal communication.

Mulago (1954): *E. Afr. med. J.*, **31**, 243.

Nigeria (1955): *Report on Nigeria for the year 1953*. Colonial Office. H.M. Stationery Office, London.

Nhonoli, A. M. M. (1954): *E. Afr. med. J.*, **31**, 1.

Platt, B. S. (1954): in *Malnutrition in African Mothers, Infants and Young Children, Report of 2nd Inter-African Conference on Nutrition*. H.M. Stationery Office, London.

Rose, J. R. (1956): *Sierra Leone Studies*, n.s. No. 6, 130. Government Printer, Freetown.

Sharpe, E. (1931): *The African Child: An Account of the International Conference on African Children*. Weardale Press, London.

Trolli, G. (1934): *Bull. Inst. colon. belg.*, **5**, 79.

Trowell, H. C., Davies, J. N. P., and Dean, R. F. A. (1954): *Kwashiorkor*. Arnold, London.

Van der Hoeven, J. A. (1956a): *Docum. méd. Géogr. trop.*, **8**, 281.

Van der Hoeven, J. A. (1956b): *Docum. méd. Géogr. trop.*, **8**, 286.

Whitbourne, D. (1930): *W. Afr. med. J.*, **4**, 3, 39.

Woodruff, A. W. (1954): in *Malnutrition in African Mothers, Infants and Young Children. Report of 2nd Inter-African Conference on Nutrition*. H.M. Stationery Office, London.

Worthington, E. B. (1938): *Science in Africa*. Oxford University Press, London.

OCCULT BLOOD IN THE VAGINA AS AN EARLY SIGN OF ORGANIC GENITAL CONDITIONS AFTER MENOPAUSE

BY

Y. M. BROMBERG, M.D.

AND

B. BERCOVICI, M.D.

From the Department of Obstetrics and Gynecology, Hadassah University Hospital, Jerusalem, Israel

VAGINAL haemorrhages occurring after the climacteric are considered of grave significance because they may indicate the presence of malignant process in the genital organs. Thus bleeding appearing one year or more after the menopause was found to be induced by malignant tumours in about a third of the cases, benign organic diseases in another third and of unknown origin in the remaining third (Corscaden, 1956). Therefore this symptom calls for careful pelvic examination and the performance of vaginal smears and cervical and/or endometrial biopsies in order to find out whether an organic lesion is present.

In a previous study we suggested that the method dependent on occult blood in the faeces currently employed in clinical medicine for diagnosis of gastro-intestinal conditions, may be also applied for detection of minimal amount of blood present in the vagina after the menopause. The modified benzidine test was used because of the great sensitivity and specificity of this method in detection of haemoglobin (Bromberg and Bercovici, 1956).

The purpose of the present investigation is to evaluate the clinical significance of the occult vaginal bleeding as an auxiliary method for early diagnosis of organic genital lesions in women after menopause.

METHOD

Needham and Simpson's (1952) modification of the Gregersen method for occult blood was adopted for detection of haemoglobin in the vagina. A mixture of 25 mg. of benzidine hydrochloride and 200 mg. of barium peroxide is dissolved in 5 ml. of glacial acetic acid in a dark glass container shortly before performing the test. A cotton-tipped stick is introduced in the vagina with a slight rotary motion. After removal, 1–2 drops of benzidine solution are allowed to fall on the cotton tip, rotating it to enable the solution to cover the entire surface. A positive reaction consists of the instantaneous appearance of a bright green colour. A weak reaction consists of the appearance of a greenish-blue colour within approximately 15 seconds. The reaction is negative when no colour appears. Care should be taken to collect specimens for occult blood before vaginal examination in order to avoid any injury of the vagina.

MATERIAL

A series of 540 patients, 43 to 70 years old, were examined for the presence of the occult blood in the vagina by the benzidine test. The duration of menopause varied from 1 to 31 years, and was spontaneous in 459 and induced by surgery or by X-rays in 81. Most of the women suffered from vasomotor disorders, vaginal discharge, vulvar pruritus, genital procidentia and backache, but in none had there been frank genital bleeding. The patients whose vaginal secretions gave positive benzidine tests were investigated further with vaginal smears or endometrial and cervical biopsies in order to determine the cause of the occult bleeding. The final diagnoses were compared with those of an equal number of consecutive patients treated for post-climacteric bleeding.

Results

Occult blood was detected in vaginal secretions of 79 out of 540 women (14·6 per cent) one or more years after the menopause, by the benzidine swab test. In all of these patients the presence of occult blood coincided with the finding of a pathological lesion of the genital organs. In those with only functional climacteric complaints the incidence of occult bleeding was 11·2 per cent, while in those with leucorrhoea it was 21·6 per cent.

The chief causes of occult bleeding were inflammatory lesions, such as atrophic vaginitis responsible for 30·3 per cent and cervical erosions responsible for 21·5 per cent of the cases of occult bleeding. Other causes were myomata of the uterus, cervical or endometrial polyps and urethral caruncles.

In 32 cases of cervical erosions 53 per cent were found to have occult bleeding and of the 164 cases of atrophic vaginitis 14·6 per cent had occult bleeding. In 2 patients malignant tumours

Table I

Incidence of Occult Vaginal Bleeding in Organic Genital Conditions after Menopause

Diagnosis	No. of Cases	Benzidine Test Positive	Frank Bleeding	Percentage of Occult Bleeding
Cervical erosions	32	17		53·1
Cervical polyp	27	7		25·9
Myoma of the uterus	41	9		22·0
Caruncle of urethra	29	5		17·2
Atrophic vaginitis	164	24		14·6
Leukoplakia of cervix	2	1		
Granulation tissue after hysterectomy	5	3		
Endometrial polyp	7	3	4	
Endometrial adenocarcinoma	5	1	4	
Carcinoma of ovary	6	1	1	
Total	318	71	9	

Table II

Relative Incidence of Causes of Frank and Occult Bleeding in Postclimacteric Women

Diagnosis	Occult Bleeding No. of Cases	Frank Bleeding No. of Cases*
Atrophic vaginitis	24	31
Cervical erosion	17	5
Myoma of uterus	9	9
Cervical polyp	7	7
Hyperplasia and proliferative endometrium	6†	13†
Caruncle of urethra	5	2
Endometrial polyp	3	4
Granulation tissue after hysterectomy	3	1
Papilloma of vagina	1	2
Vaginal lacerations due to pessary	1	–
Leukoplakia of cervix	1	–
Endometrial adenocarcinoma	1	4
Adenocarcinoma of ovary	1	1
Total	79	79

* Consecutive cases of frank bleeding equal in number to those of occult bleeding.

† 2 cases due to exogenous oestrogens.

were found, one case of endometrial adenocarcinoma and one case of adenocarcinoma of ovary with uterine invasion (Table I).

When the causes of frank genital bleeding were compared with those of occult bleeding in two equal series of patients, in both groups the most frequent lesion was atrophic vaginitis (endometrial biopsies showing atrophic endometrium and vaginal smears various degrees of vaginal atrophy). Cervical inflammatory conditions were more frequent in the series with occult bleeding, while hyperplastic and proliferative endometrium were more frequently found in the series with frank bleeding. The finding of occult uterine bleeding led to the detection of one case of adenocarcinoma, while frank bleeding led to the diagnosis of uterine carcinoma in 4 cases (Table II).

Comment

The benzidine test is a highly sensitive and specific reaction for the detection of haemoglobin. Positive reactions have been obtained in dilutions of blood in saline or water up to 1:320·000 (Bromberg and Bercovici, 1956). When the reliability of the benzidine test for the detection of blood in vaginal secretions was compared with that of microscopic examination, the test was found to be positive even in cases in which only 1–2 erythrocytes could be seen per high power microscopic field. In some cases the reaction was positive when no blood cells at all could be detected in vaginal smears. In such cases it was thought that red blood cells had been haemolyzed by the low vaginal pH, bacteria or lysins present in vaginal secretions. Leucocytes, exfoliated cells, trichomonads, monilia and spermatozoa in vaginal secretions do not react with benzidine.

Blood pigment was not found in vaginal secretions of normal healthy post-climacteric women. When occult bleeding was found it was always possible to identify an organic lesion as the probable source of the bleeding.

The high incidence of occult bleeding in cases of atrophic vaginitis (14·6 per cent) is in accordance with the frequent clinical observation of blood-tinged vaginal discharge in this condition. The comparatively high incidence of occult vaginal bleeding found in our patients was chiefly due to the fact that so many of them complained of leucorrhoea as a manifestation of atrophic vaginitis or cervical erosions which often gave positive benzidine tests. The whitish-yellow discharge in many of them contained significant amounts of occult haemoglobin.

Endometrial carcinoma was found in 4 out of 79 patients suffering from frank bleeding, and in 1 patient in whom uterine bleeding could only be revealed by the benzidine test. It should be noted that in our cases of frank uterine bleeding the incidence of the malignant genital neoplasms is low (5 out of 79) when compared with data published elsewhere: 27·5 per cent by Brewer and Miller (1954) and 33 per cent by Israel and Weber (1956). This relatively low incidence of uterine carcinoma as a cause of post-climacteric bleeding in Jewish women in Israel has been previously reported (Brzezinsky and Bromberg, 1953).

On comparing the causes of occult bleeding with those of frank genital bleeding in post-menopausal women no striking difference was found. The greater incidence of hyperplasia of the endometrium as a cause of frank bleeding and of cervical erosions as a cause of occult bleeding, are in keeping with the amount of blood loss one would expect in these conditions.

The results of our study demonstrate that the finding of occult blood in vaginal secretions of post-menopausal women points to an organic lesion of the genitalia. In our experience, patients whose vaginal secretions give a positive benzidine test require thorough investigation including endometrial and cervical biopsy and vaginal smear, in order to determine the cause of this minor haemorrhage.

Summary

The modified benzidine test is a practical method for detecting minimal vaginal bleeding occurring after the menopause. A positive benzidine test in vaginal secretions was found in 14·6 per cent of 540 women one year or more after the menopause.

In all patients with occult vaginal blood, an organic genital lesion was diagnosed. The most frequent cause of the minimal genital bleeding

was atrophic vaginitis and other inflammatory conditions. In 2 cases genital malignancy was found.

It is suggested that detection of occult genital bleeding by the benzidine test may aid in the early diagnosis of neoplasms in post-climacteric women.

References

Brewer, J. I., and Miller, W. H. (1954): *Amer. J. Obstet. Gynec.*, **67**, 988.

Bromberg, Y. M., and Bercovici, B. (1956): *Exp. Med. Surg.*, **14**, 134.

Brzezinsky, A., and Bromberg, Y. M. (1953): *Obstet. Gynec.*, **1**, 359.

Corscaden, J. A. (1956): *Gynecologic cancer*. 2nd edition. Williams and Wilkins, Baltimore.

Israel, S. L., and Weber, L. L. (1956): *Obstet. Gynec.*, **7**, 286.

Needham, C. D., and Simpson, R. G. (1952): *Quart. J. Med.*, n.s. **21**, 123.

A STUDY OF OBSTETRIC RESULTS IN AN UNDER-DEVELOPED COMMUNITY

Part I—(a) The Objects, Materials and Methods of the Study (b) Some Comparative Rates

BY

ZENA STEIN, M.A., M.B., B.Ch.(Rand.)

AND

MERVYN SUSSER, M.B., B.Ch.(Rand.), M.R.C.P.E.

Department of Social Medicine, Manchester University

Lately of Alexandra Health Centre and University Clinic, Johannesburg

RECENT studies of perinatal mortality in socially developed communities have thrown light on the causes and prevention of infant deaths. We have attempted a similar study in a socially under-developed community, both to compare causes which are common to all communities and to establish others which are specific to this one. We hoped that from this analysis there might emerge the knowledge and means for reducing obstetric mortality in such a community.

The approach is from four aspects.

Firstly we give the death rates associated with childbirth in Alexandra Township, Transvaal, and compare these with those of other communities in order to describe the existing position. It is hoped that these figures will prove useful in themselves; there is very little in the literature which can be used for comparative purposes and one must presume that the general picture for communities of this type is hardly known.

In a second paper we analyze, with reference to these death rates, the incidence and importance of certain relevant factors for this community. Although these factors are not usually considered, it is essential, when comparing figures from countries as different as those discussed, to take some of these into account. The outstanding examples here, apart from age and parity, are twins and the Rhesus factor.

A third paper will describe the criteria used for hospital admissions in a community served by a domiciliary practice where hospital beds are neither near nor plentiful. The results obtained in this way, the degree to which they might be improved, and their close dependence on antenatal work are examined. The disasters, considering the general conditions, were few—much less than those due to other and, we think, more easily preventable causes.

Fourthly, we assess the midwifery service, especially with regard to the place of delivery and the assistance available at birth, against the cultural background of the community. In this way, we have tried to isolate some effects of cultural factors and to establish their very great importance in this community. We have been able to show the value of a domiciliary service in Alexandra, in that results are greatly inferior for unattended births. The first remedy is to bring births that now occur without clinic help within reach of the clinic.

This study of obstetric results has emphasized the necessity, when planning health services in a community like this, to see midwifery as part of the total problems of community health. It is clear from our analysis that in Alexandra a relatively cheap and simple domiciliary midwifery service can maintain low obstetric death rates; also that further improvement in these can come from a closer and more sustained

contact with the mothers. Closer contact and more health education would be the most rewarding measures in this community, and these measures would be equally effective in combating the extremely high infant mortality rates (Kark and Cassel, 1952). Alexandra needs more workers in the field—practitioners of social medicine who will study both community and individual, anthropologists or sociologists, and health educators whether in their own right or disguised as clinicians, health visitors, district nurses or social workers. These will save lives where more traditional institutions can contribute little.

Alexandra Township

Alexandra Township is eight miles from the centre of Johannesburg. Most of its 20,000 African families live in extreme poverty. Malnutrition is widespread. Homes are slums and greatly overcrowded, sanitation is lacking and typhoid and dysentery are endemic (Alexandra Township, 1954). Education has provided bare literacy or less in many families. Some families have lived in Alexandra for two generations, others are recent arrivals, but almost all retain vestiges of tribal beliefs and superstitions which have survived their "education".

Recent studies (Woolf, 1947; Crosse, 1952; Duncan, Baird and Thomson, 1952; Morris and Heady, 1955) demonstrate a close connexion between social factors and obstetric risks. These factors are even more important in an impoverished and under-developed community, and we found in Alexandra that a study of obstetric deaths could not be isolated from the salient problems of poverty and ignorance.

The Alexandra Health Centre and University Clinic (A.H.C. and U.C.)

The A.H.C. and U.C. (Susser *et al.*, 1955) conducts a maternity service, as well as providing the main consulting and home-visiting service in Alexandra. The midwifery service concerns three groups of mothers:

Firstly, those mothers who attend the antenatal clinic and are delivered and nursed postnatally in their homes by trained African midwives from the A.H.C. and U.C. (Clinic deliveries), 1,212 cases.

Secondly, those who attend antenatal clinics but are referred for delivery and postnatal care to the maternity hospital (Hospital deliveries), 165 cases.

Thirdly, those who attend antenatal clinics but who deliver themselves without trained assistance in their homes (i.e., births before the arrival of the midwife). These mothers are also nursed during the postnatal period (Unassisted deliveries), 754 cases.

Results from these three groups together have been used to assess the overall rates for obstetric deaths. The antenatal clinics, which also include all three groups of mothers, have provided most of the material for the second part of this study. For the assessment of the service, we have compared the groups with each other. Unavoidable difficulties account for the lack of certain desirable analyses, e.g., the age and parity of mothers for unassisted births.

Some Comparisons of Obstetric Results

The rates for Alexandra are based on the records of 2,134 mothers attending the A.H.C. and U.C. who were confined during 1954. They comprise about two-thirds of all the women confined in Alexandra during that year and are representative of Alexandra mothers for economic status, tribe, age and parity (Navid, 1955). 1954 was not an exceptional year and available figures for 1952 and 1953 are very similar.

We have compared death rates in Alexandra with those for the United States and for Great Britain.

Stillbirths (Table I)

There were 76 stillbirths among these mothers.

It will be seen that the stillbirth rates for Alexandra compare well with those for Social Class V in England and Wales, 1949. (The effects of illegitimacy in Alexandra could not be excluded, as they are for Social Class V. In a society as fluid as Alexandra, the definition of illegitimacy presents a major problem and births illegitimate on strictly legal grounds form a great proportion of all births.)

TABLE I

Stillbirth Rates for Various Populations

Population	Year	Stillbirth Rate per 1,000
Total Alexandra	1954	34·6
Total Alexandra excluding multiple births	1954	27·2 (of single births)
England and Wales	1941	35
England and Wales	1949	22·7
England and Wales	1954	23·5
England and Wales Social Class V, excluding multiple and illegitimate births	1949	25·4 (of single births)
United States—non-white	1954	28·9
United States—whites	1954	15·5

TABLE II

Clinical Causes of Stillbirths by Age and Parity

Cause	Total No. of Still-births	Age				Parity		
		U.20	20–29	30+	Un-known	0	1–4	5+
Complications of labour (mal-presentation 7, inertia 2, dis-proportion 3, prolapsed cord 4, ante-partum haemorrhage 1, abruptio placentae 1)	18	2	8	7	1	4	7	7
Toxaemia	10	2	2	4	2	3	3	4
Foetal abnormality	1	0	1	0	0	1	0	0
Congenital syphilis	2	1	0	0	1	0	2	0
Mature, cause unknown (5 macerated, 5 fresh)	10	2	5	2	1	4	5	1
Premature, cause unknown	6	0	5	1	0	1	4	1
Unassisted labour, mature, cause unknown	11	0	5	4	2	0	8	3
Twins (18 stillbirths, 14 mothers)	18	0	10	6	2	2	11	5
Totals for all causes	76	7	36	24	9	15	40	21
Total number of mothers	2,134	182	1,003	325	624	389	1,424	321
Stillbirth rate per 1,000 total births*	35·6	38·5	35·9	73·8	14·42	38·6	28·1	65·4

* The distribution by age and parity for all confinements is given in a later paper. The unknown age group is selected in that special efforts were made to ascertain age of mother in stillbirths.

Comparative figures for whites and non-whites in the United States suggest no racial superiority for non-whites, although this is only a very rough guide, the non-white American group being a compound of West Africans and several other ethnic groups, including Asiatics.

Clinical Causes of Stillbirths (Table II)

The clinical causes of stillbirths are similar to those reported in studies elsewhere (Baird, Thomson and Duncan, 1953; Crosse and Mackintosh, 1954) save for a group which we have been obliged to add to the tally, viz.,

"Unassisted labour, mature, cause unknown".

The age-group 30+ and the parities above 5 appear at a marked disadvantage. The causes contributing to deaths in these groups are twins, complications of labour, toxaemia, and "unassisted labour, mature, cause unknown". Toxaemia appears to cause stillbirths mainly in older multiparae, and this is in agreement with the findings of Nelson (quoted by Baird, Thomson and Duncan, 1953) and of Dieckmann (1952). Unassisted labour and twin obstetric deaths can be attributed largely to cultural factors, which, we believe, operate particularly among older women. These factors are discussed in a later paper.

Primiparae formed 18 per cent of the population and their stillbirths account for 18 per cent of the total. They do not appear at a disadvantage probably because of their youth (see Part II), just possibly because they were admitted to hospital out of proportion to their numbers, and perhaps mainly because of their much readier assimilation of the ideas (or rituals) of scientific medicine.

First Week Deaths

There were 31 first week deaths. Table III makes some comparisons.

TABLE III

Comparisons of First Week Deaths for Different Populations

Population	Year	Death Rate (per 1,000 live births)
Alexandra total	1954	14·6
England and Wales ..	1954	14·6
United States—non-white ..	1954	22·6

Alexandra rates are not worse than those for England and Wales. There appears to be some shift from first week deaths to stillbirths as compared with the figures for England and Wales.

Youthful maternities, high parity and poverty have been thought to account, in part at least, for the differences shown in England for first week death rates between Social Class V and Social Class I. These features are all more marked in our African groups than in Social Class V. One must presume, in the face of the comparatively favourable results for Alexandra, that other cultural and biological factors are keeping the rates down. (Later we will show some that are keeping them up.)

Table IV shows the distribution of first week deaths by clinical causes.

TABLE IV

Clinical Causes of First Week Deaths

Prematurity, cause unknown	14
Twins	2
Rh incompatibility	1
Birth trauma	6
Toxaemia	2
Mature, cause unknown	6
Total	31

Prematurity accounts for 45 per cent of all the first week deaths and is the major cause of first week deaths in each parity group. Premature births in Great Britain (Douglas, 1950) accounted for 52 per cent of all neonatal deaths (i.e., of babies up to 4-weeks old); in Birmingham (Crosse and Mackintosh, 1954) for 62 per cent; and in Liverpool (Capon, 1955) for 59 per cent.

*Obstetric Deaths Rates**

The number of obstetric deaths (using this term to mean the sum of stillbirths and first week deaths (Baird *et al.*, 1953)) was 107, giving a rate of 48·8 per 1,000 total births, and of 40·8 per 1,000 excluding twins. The rate for booked cases, excluding twins, for Aberdeen Maternity Hospital, 1938–52 was 38·6 (Baird, Walker and Thomson, 1954). This hospital delivered one-quarter of all Aberdeen mothers in 1939, and three-quarters in 1950, so that the figures give an idea of obstetric deaths in the community (Baird *et al.*, 1953).

There has been a steady reduction in obstetric death rates in England and Scotland over the last decade. Duncan, Baird and Thomson (1952)

* We have avoided the term perinatal because of the different meanings at present given to this word.

attribute the decrease in deaths to raised standards of nutrition, health education and medical facilities. Most Alexandra mothers are malnourished but we cannot tell from our data how nutrition affects their pregnancies. However, from our records of obstetric deaths we can assess the effect of health education and of midwifery services in preventing obstetric deaths, and this we do later.

Maternal Death Rate

Of 7,177 confinements of mothers attending the A.H.C. and U.C. during 1952, 1953 and 1954, there were 7 maternal deaths, an incidence of 0·97 per 1,000 mothers—as compared with 0·59 (1954) in England and Wales.

Comment on Obstetric and Maternal Death Rates

These figures reflect a domiciliary service in homes which would be considered unsuitable for confinement by any usual standards. In addition it has been shown by Heyns (1944, 1945) that Alexandra women are at a mechanical disadvantage (as against white mothers) when the size of the pelvis is compared with the size of the baby's head. When these facts are considered together with the great poverty of the people of Alexandra, the non-scientific culture, the ignorance and malnutrition, it is surprising that the obstetric rates compare so well with those of Great Britain.

It has been suggested with force by Heyns and Shippel (1946) that Alexandra women may profit from relaxed labour in their homes. Such psychological effects and, of course, conditions in general, require separate assessment for each community. A domiciliary service is probably the most effective service at present possible in Alexandra.

Baird (1945) compared stillbirth and neonatal death rates with infant mortality rates in Holland, England and Scotland and noted that stillbirth rates were high where infant mortality rates were high. (Table V.)

Clearly, Baird's generalization does not apply in a simple way to our community. The infant mortality figure reflects more closely the poor circumstances of the population, while the stillbirth rate, although surely not unrelated to this, is affected as much by age and parity, and by the absence of skilled assistance at the confinement, but also by other favourable biological and cultural effects still to be elucidated.

When seen against the total situation in Alexandra, the obstetric rates are better than one might have expected. We are not in a position to pursue all the causes for these results and there is room for research in this direction.

In spite of this favourable appearance, a high proportion of the obstetric deaths are obviously preventable in the light of present medical knowledge. In our view their prevention can best be achieved through the already effective domiciliary service and health centre.

Summary

(1) One hundred and seven obstetric deaths occurring among 2,134 confinements in Alexandra Township, Johannesburg, during 1954 are analyzed.

(2) The stillbirth rate of 34·6 per 1,000 total births is compared with that for other populations. The clinical causes of stillbirths in Alexandra are similar to those given for British

Table V

Comparison of Stillbirth and Neonatal Death Rates for Different Populations

Population	Holland (1938)	England (1938)	Scotland (1938)	Alexandra (1954)
Stillbirths	25	38	42	35
Neonatal deaths	21	27	35	15 (1 week only)
Infants 1–12 months ..	15	21	31	200*

* Annual Report A.H.C. and U.C. for 1954.

towns, save for the additional group in Alexandra of "Unassisted births, cause unknown". There is a sharp increase in rate for older women and women of high parity.

(3) The first week death rate in Alexandra is 14·6 per 1,000 live births, as is the rate for England and Wales for 1954. Analysis of the clinical causes of first week deaths in Alexandra, as in English cities, shows prematurity to be a major factor.

(4) The obstetric death rate for single births in Alexandra was 41 per 1,000 total births; that for Aberdeen Maternity Hospital, 1938–52 was 38·6.

(5) The maternal mortality rate for Alexandra over the years 1952–54 (7,177 pregnancies) was 0·97 per 1,000; that of England and Wales for 1954, 0·59 per 1,000.

(6) In spite of the apparently favourable midwifery results, further analysis will show a high proportion of the obstetric deaths to be preventable in the light of present medical knowledge. In our view, they can best be prevented through the already effective domiciliary service and health centre.

Acknowledgments

We wish to record our close co-operation in this work with our colleagues, Dr. M. A. Cormack and Dr. M. K. S. Hathorn. We are indebted to the clerks of the Alexandra Clinic, Mr. T. Mtembu, Mr. J. Seeco and Mr. P. Pheto, and to Sister M. M. Stanton and the midwives. Mrs. P. Frost and Miss C. Frost helped in the analyses.

References

Alexandra Township (1954): *Report of the Medical Officer of Health.*

Baird, D. (1945): *J. Obstet. Gynaec. Brit. Emp.*, **52,** 339.

Baird, D., Thomson, A. M., and Duncan, E. H. L. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60,** 17.

Baird, D., Walker, J., and Thomson, A. M. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61,** 433.

Capon, N. B. (1952): *Brit. med. J.*, **1,** 805.

Crosse, V. M. (1952): *The premature baby.* Churchill, London.

Crosse, V. M., and Mackintosh, J. M. (1954): *in* Gairdner, D. (ed.): *Recent advances in paediatrics.* Churchill, London. p. 63.

Dieckmann, W. J. (1952): *The toxemias of pregnancy.* 2nd edition. Kimpton, London.

Douglas, J. W. B. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57,** 143.

Duncan, E. H. L., Baird, D., and Thomson, A. M. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59,** 183.

Heyns, O. S. (1944): *J. Anat., Lond.*, **78,** 151.

Heyns, O. S. (1945): D.Sc. Thesis, Univ. Witwatersrand.

Heyns, O. S., and Shippel, S. (1946): *J. Obstet. Gynaec. Brit. Emp.*, **53,** 519.

Kark, S. L., and Cassel, J. (1952): *S. Afr. med. J.*, **26,** 101, 132.

Ministry of Health (1950–1957): *Reports of the Chief Medical Officer, 1949–1956.* H.M. Stationery Office, London.

Morris, J. N., and Heady, J. A. (1955): *Lancet*, **1,** 343.

Navid, H. (1955): *A social survey of Alexandra Township* (unpublished).

Susser, M. W., Stein, Z. A., Cormack, M. A., and Hathorn, M. K. S. (1955): *Lancet*, **1,** 912.

United States Department of Health, Education and Welfare (1957): *Vital statistics, Special reports*, **44,** 10.

Woolf, B. (1947): *Brit. J. soc. Med.*, **1,** 73.

A STUDY OF OBSTETRIC RESULTS IN AN UNDER-DEVELOPED COMMUNITY

Part II—The Incidence and Importance of Certain Factors with Bearing on Obstetric Death Rates

BY

MERVYN SUSSER, M.B., B.Ch.(Rand.), M.R.C.P.E.

AND

ZENA STEIN, M.A., M.B., B.Ch.(Rand.)

Department of Social Medicine, Manchester University

Lately of Alexandra Health Centre and University Clinic, Johannesburg

ALEXANDRA is a typical under-developed South African community (Susser, 1957). To understand the obstetric death rates, it is necessary to know the distribution of ages and parities among Alexandra mothers. These are not the only biological factors which vary widely from one population to another, and in this paper we also discuss the effect of twinning, the Rhesus factor and prematurity. Prematurity should perhaps be thought of with other nosological factors like toxaemia and syphilis. In this paper, we have analyzed the extent to which all these factors are important in Alexandra—the biological factors must affect our evaluation of the local rates and the local services, while the nosological factors should direct our thinking about preventive work.

AGE AND PARITY

TABLE I

Age and Parity of 2,134 Alexandra Mothers

Age	Parity 0	Parity 1–4	Parity 5+	Total
Under 20 ..	135	47	0	182
20–24 ..	92	410	4	506
25–29 ..	49	401	47	497
30+ ..	8	145	172	325
Not known* ..	105	421	98	624
Totals ..	389	1,424	321	2,134

* In these cases the mother was unable to state her age, but taken by parity the distribution is random.

More than a third of all primigravidae were under 20 years old, and only 8 (i.e., 2·8 per cent) are "elderly". Salber and Bradshaw (1953) found 1·1 per cent of their African primigravidae confined in a Durban hospital to be 30 years and over, while, of their white South African primigravidae, 18·2 per cent were over 30 years.

Two hundred and twenty-three Alexandra mothers (14 per cent) were of parity 5 or more. Salber and Bradshaw (1953) found 21·2 per cent of their African mothers in Durban had a parity of 4 or more and 5·4 per cent of their white mothers fell into this group. Figure 1 shows the age and parity distribution for Alexandra mothers compared with that for England and Wales, 1949 (Daly, Heady and Morris, 1955). The trend in Alexandra is towards larger families for younger mothers.

THE INCIDENCE AND IMPORTANCE OF MULTIPLE PREGNANCIES IN ALEXANDRA

There were 60 twin confinements in 2,134 births under the A.H.C. and U.C. in 1954. Sixty twin confinements were recorded among 2,152 births from Alexandra during 1953. Of 2,444 consecutive booked confinements in a Johannesburg African Maternity hospital, 54 twin confinements are recorded (Bridgman Memorial Hospital, 1954).

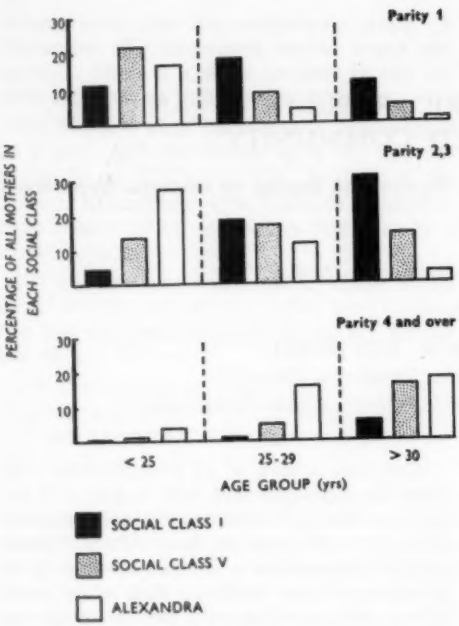


FIG. 1

To show the age and parity distribution of Alexandra mothers as compared with the distribution for Social Classes I and V in England and Wales. (Taken from Daly, C., Heady, J. A., and Morris, J. N., 1955.)

Of these 6,730 confinements, covering a similar population of urban African mothers in the Johannesburg area, the incidence of twin pregnancies is 1 in 39. Table II gives some twinning rates by age of mother for different populations (Enders and Stern, 1948).

TABLE II

Twinning Rates for Different Races by Age of Mother: Incidence per 1,000 Births

Age of Mother Years	U.S.A. Negroes	U.S.A. Whites	Alexandra 1954
Under 20 ..	6·4	5·7	5·5
20–24 ..	10·8	8·2	27·7
25–29 ..	15·9	11·0	22·1
30–34 ..	20·6	14·2	35·3
35–39 ..	24·3	17·0	54·3
40+	17	14·1	94·3

The over-all twinning rate in Alexandra (28 per 1,000 in 1954) is seen to be high in comparison with other populations, and the same trend of increasing rates with age is seen. The number of Alexandra mothers bearing twins is only 60 and only 53 women among all the 2,134 maternities in 1954 were over 40 years. Thus the small size of the sample will reduce the reliability of the figures given above.

From an examination of the numbers of like and unlike sexes among the twins born in 1954, it was calculated that almost all twins in this population are binovular. This would agree with the supposition that the incidence of monovular twins is more or less constant for different populations, and is only about 3 per 1,000 births. The rates for binovularity show a considerable variation, though we have not so far seen figures as high as those given above for Alexandra.

Anthropological studies might throw light on the variability of the binovular twinning trait among the different human groups. Twinning, because of the high stillbirth and infant mortality rates associated with it, might not have been as successful (not even half as successful) as single births under primitive conditions of child-rearing. The Shangaans, who formed a considerable proportion of Alexandra mothers (13 per cent), are known in their tribal culture to expose one twin at birth, and rear the single survivor. One might surmise that by their giving one twin a reasonable chance of survival, the twinning trait was better able to perpetuate itself in their society.

Because the incidence of twins is high, the obstetric problems of twins are of great importance.

The Obstetric Problems of Twins

Of 60 confinements in Alexandra in 1954, there were 18 stillbirths and 2 first week deaths, i.e., 20 obstetric deaths.

The obstetric death rate of 166·6 for twins contrasts with the rate of 40·8 for the single births.

In 90 twins where the birth weight was recorded and available the average weight was 5 pounds 7 ounces. Only 31 babies of the 90 were under 5½ pounds (a proportion which, by

analogy with results for prematures, is probably a good deal too low).

Russell (1952) found an obstetric death rate of 80 per 1,000 among Aberdeen nursing home twins and 160 per 1,000 among Aberdeen Maternity Hospital twins. He thought that poor diet might be a factor in twin mortality and malnutrition is endemic in our community. The age and high parity of the twin mothers will also play a part in the high death rate. Lack of skilled assistance at birth, however, in deliveries fraught with complications, was the decisive factor for Alexandra twins.

The Incidence of Prematurity

We have records of only 108 premature births during 1954, 77 among single births and 31 among twins. The incidence, excluding twins, is 3·7 per cent. This is certainly an underestimate, probably due to inaccurate scales and weighing in the homes. The probable rate is 10–12 per cent (Salber and Bradshaw, 1951; Bridgman Memorial Hospital, 1954).

There is nothing to suggest that prematurity, in the depressed social setting of Alexandra, is making an unexpected contribution to the obstetric death rate (Crosse, 1952; Kahn, Wayburne and Fouche, 1954).

Syphilis

The pathogenesis of syphilis in urban Africans (Kark, 1949; Sax, 1951) is a historical and social process bound up with the absorption of tribal men into the mine compounds and the resulting distortion of masculinity rates, the growth of the migrant labour system and the break-down of family life. Routine serological tests done at Alexandra during 1954 showed an incidence of 18 per cent positives among pregnant mothers, but there has been a steady fall over the last few years.

In this series we thought congenital syphilis to be the cause of only two stillbirths out of 76 among clinic deliveries. In both cases the mother came to the antenatal clinic at an advanced stage of pregnancy and delivered herself before she had received treatment. There were no other obstetric deaths due to syphilis although the number of infected mothers is high.

The antenatal sessions can, through education, explanation and thorough treatment, play a part as well in reducing the overall incidence of syphilis in the community. The A.H.C. and U.C. could, in its general out-patient work, do more on this aspect of prevention. With the many social forces operating to keep syphilis alive and spreading, however, it is likely for long to have a formidable incidence in African communities in South Africa.

Rh Incompatibility

Of 1,913 mothers in whom the Rh factor was known in 1954, 4·2 per cent were Rh negative, which is close to the generally accepted figure of 5 per cent for Africans in South Africa (Zoutendyk, 1947). This contrasts with the incidence of 15 per cent for South African whites, and 7–9 per cent for American coloured people. The Japanese have an incidence of 2 per cent and the American Chinese slightly less (quoted by Altmann and Lewis, 1945).

The incidence of anti-Rh antibodies and of erythroblastosis in Alexandra was also considered. Whereas Mollison, Mourant and Race (1952) quote an incidence of 1 case of haemolytic disease for every 200 (0·5 per cent) pregnancies in Great Britain, where the incidence of Rh negative women is 15 per cent, we found only 3 possible cases among 4,286 consecutive pregnancies, or 0·07 per cent. A detailed examination of the obstetrical histories of all Rh negative women during 3 years disclosed no further cases. This comparatively low rate of haemolytic disease may be accounted for by the character of the Rh components (Zoutendyk, 1947).

Antibodies were found in 2 mothers in 1954. In one case exchange transfusion soon after birth was accomplished in hospital and the infant survived. The other baby died a few minutes after birth, before transfusion could be given.

Rh incompatibility is seen to be a problem affecting very few mothers in our community.

Toxaemia

We found it unprofitable to estimate an incidence of pre-eclampsia since diagnostic

standards vary and our records proved unsuitable; but we do have certain observations for Alexandra.

(1) Pre-eclamptic toxaemia was the primary cause of hospital admission in 23 mothers, in 1954. Out of the total of 2,134 mothers many others, however, were treated in their homes for this condition.

(2) Pre-eclamptic toxaemia was thought to be the major cause of death in 12 out of 76 stillbirths in 1954, and an associated complication in 4 others.

(3) No maternal deaths were attributed to toxaemia during the period 1952–54 (7,177 consecutive confinements) although some mothers were gravely ill with coma and fits. In 1954 there were 2 cases of eclampsia, an incidence of 0·1 per cent.

(4) A Johannesburg maternity hospital for Africans gives an incidence for "toxaemia of late pregnancy" among booked cases of 8·9 per cent (Bridgman Memorial Hospital, 1954).

These data are enough to indicate that toxaemia is a grave factor in Alexandra midwifery. Comparative figures for the incidence of eclampsia in different countries show a great range (Dieckmann, 1952): in the

British Isles (1947–1950)	0·632	per cent of all mothers have eclampsia.
Copenhagen	0·17	per cent of all mothers have eclampsia.
Uganda	0·1	per cent of all mothers have eclampsia.
New Zealand	0·56	per cent of all mothers have eclampsia.

The incidence of 0·1 per cent for Alexandra is low. On the other hand, we attributed 12 obstetric deaths (out of 107) to toxaemia, while Baird, Walker and Thomson (1954) assess toxaemia to be the cause of 10 per cent of their obstetric deaths, a figure very close to ours.

Thus, while the incidence of eclampsia seems relatively low, non-convulsive toxaemia is responsible for a considerable number of obstetric deaths. On examining the records, it becomes obvious that we sometimes acted tardily, especially in arranging hospital admissions. Indeed some hold that toxaemic cases cannot be treated as out-patients or in their homes (Dawson, 1953). Increased vigilance would, we believe, prevent some obstetric deaths due to toxaemia.

Conclusion

It will be seen that Alexandra women are favoured by the biological factor of youthful childbearing, as well as by a low rate of Rh negativity, although they are handicapped by high parities. In the prevailing social conditions, twinning, which is twice as common as in England, and prematurity are serious disadvantages. Syphilis is widespread, but, in spite of its perpetuation by social conditions, most of its obvious obstetric effects can be prevented. While eclampsia is infrequent, obstetric deaths due to toxaemia are not, and good medical care should reduce these.

Taking the overall obstetric death rates for Alexandra (given in an earlier paper) we may suspect that there are biological and other factors as yet not demonstrated which operate in favour of Alexandra women. The effects of medical care on these rates will be discussed in a later paper.

Summary

The influence of various biological and nosological factors on obstetric rates in Alexandra, South Africa, which is an under-developed urban community, is assessed.

(1) Age and Parity: More than one-third of primigravidae are under 20 years and only 2·8 per cent over 30. Alexandra rates are favoured by this, although handicapped by high parities. Fourteen per cent were of a parity of 5 or more.

(2) One of every 40 pregnancies was a twin pregnancy. The obstetric death rate for twins was 166·6 per 1,000, and unassisted births contributed to this high rate. Older women of high parity were likely to have twins and to choose unassisted births.

(3) Prematurity, estimated at 10–12 per cent, probably has no unexpected effects in the prevailing social conditions.

(4) Eighteen per cent of mothers had positive serological reactions to syphilis, but only 2

obstetric deaths were attributed to congenital syphilis. The disease is not being prevented as it should be although its obstetric effects are.

(5) Three in 4,286 mothers (0·07 per cent) gave birth to infants with haemolytic disease due to Rh incompatibility. Of Alexandra mothers 4·2 per cent were Rh negative. In Alexandra Rh incompatibility is a negligible cause of obstetric deaths.

(6) The incidence of eclampsia is low in Alexandra but stillbirths associated with pre-eclamptic toxaemia were no fewer than for Aberdeen.

Acknowledgments

We wish to record our close co-operation in this work with our colleagues Dr. M. A. Cormack and Dr. M. K. S. Hathorn. We are indebted to the clerks of the Alexandra Clinic, Mr. T. Mtembu, Mr. J. Seeco and Mr. P. Pheto, and to Sister M. M. Stanton and the midwives. Miss Helen Navid and Miss Esther Nkopo undertook the investigation of twin mothers. We have to thank Mr. M. Bulmer for statistical assistance with the data on twins.

References

Altmann, A., and Lewis, G. E. (1945): *S. Afr. J. med. Sci.*, **10**, 137.

Baird, D., Walker, J., and Thomson, A. M. (1954): *J. Obstet. Gynaec. Brit. Emp.*, **61**, 433.

Bridgman Memorial Hospital (1954): *Annual report.* Johannesburg.

Crosse, V. M. (1952): *The premature baby.* Churchill, London.

Daly, C., Heady, J. A., and Morris, J. N. (1955): *Lancet*, **1**, 445.

Dawson, B. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 80.

Dieckmann, W. J. (1952): *The toxemias of pregnancy.* 2nd edition. Kimpton, London.

Enders, T., and Stern, C. (1948): *Genetics*, 33.

Kahn, E., Wayburne, S., and Fouche, M. (1954): *S. Afr. med. J.*, **28**, 453.

Kark, S. L. (1949): *S. Afr. med. J.*, **23**, 77.

Mollison, P. L., Mourant, A. E., and Race, R. R. (1952): *Med. res. Counc., Lond.*, Memo. No. 27.

Russell, J. K. (1952): *J. Obstet. Gynaec. Brit. Emp.*, **59**, 208.

Salber, E., and Bradshaw, E. S. (1951): *Brit. J. soc. Med.*, **5**, 113.

Salber, E., and Bradshaw, E. S. (1953): *Brit. J. soc. Med.*, **7**, 20.

Sax, S. (1951): M.D. Thesis, Univ. Witwatersrand.

Susser, M. W. (1957): *Med. World*, **86**, 385.

Zoutendyk, A. (1947): *S. Afr. J. med. Sci.*, **12**, 167.

THE PLACENTAL SEPTA

A Study Based Upon Nuclear Morphological Sex Differences

BY

DAVID M. SERR, M.B., Ch.B.

ARYEH SADOWSKY, M.D.

AND

GERTRUDE KOHN, B.A.

Department of Obstetrics and Gynaecology, Rothschild-Hadassah University Hospital and the Hormone Research Laboratory, Hebrew University-Hadassah Medical School, Jerusalem, Israel

THE human placenta is divided into about 15–20 cotyledons, these divisions being visible on its maternal surface. Between the cotyledons, there extends a groove deep into the placental tissue in which lies a thin membrane, the placental septum, whose origin and composition has long been the subject of controversy.

This membrane does not reach to the chorionic membrane, and does not form a complete separation between two cotyledons. On the average, however, it covers more than half the depth of the intercotyledon groove, and it is to be seen most easily from the side of the decidual plate.

Grosser (1927) reviewed the varying opinions then held as to whether the septum is of maternal or foetal origin. He was of the opinion that the part of the septum nearest to the maternal surface can be found to contain decidual cells, and that most of the rest of the septum is an empty network, into which trophoblastic cells have invaded. He thinks that many septa, towards the end of pregnancy, especially those parts distant from the decidual plate, are composed of foetal elements. Schroeder (1930) also stated that the septum was of foetal origin.

More recently, other investigators have continued the controversy, and in the *FIAT Review of German Science* (1948) the statement is made that the septa are undoubtedly foetal in origin, an opinion agreed to by Stieve (1940).

Eastman (1956) has described the placental septa as being made up of trophoblastic cells, fibrous tissue, and some arteries and veins. Whilst he is of the opinion that they are foetal in origin, he states that what few blood vessels they contain must be mat rnal.

Wislocki (1956), basing his opinion upon his histochemical and electron microscope findings and upon the observations of Spanner (1935), Stieve and von der Heide (1941), regards the septum as foetal rather than maternal. He did not even find a core of maternal tissue in the septa placentae, although he agrees that such a core may have been existent very early or during the development of the placental septa. Another opinion in favour of a trophoblastic origin has recently been expressed by Latta and Beber (1957). In spite of this, other authors, discussing the origin of the septa, are of the opinion that the finding of maternal blood vessels in the septum suggests a maternal origin. Ramsay (1956) suggests a comparison with the findings in the monkey. In this animal's placenta there is a brief excursion of the maternal vessels into the septum, and because of this finding she believes there must be at least some maternal tissue in the septa.

Boyd (1956) concurs with this opinion, stating that he is sure there is an extension of decidua into the septum, only a part of it being derived from the cytotrophoblast. Greenhill (1955) states that the maternal surface of the placenta is divided by decidual septa into numerous lobes

called cotyledons. Similarly, Petchenko (1956) has recently expressed the opinion that the septa are of maternal origin.

The methods used until now as a means of differentiating cytotrophoblast from maternal cells have been based upon histological, histochemical and electron microscope studies. The purpose of the present study was to attempt to determine the origin of the placental septum by applying the method of identifying the sex of non-dividing cells by a study of the morphological difference in their nuclei. This method, described originally by Moore, Graham and Barr (1953), and now popularly known as "nuclear sexing" is based upon the difference in the percentage of cells containing sex chromatin bodies (chromocentres) in their nuclei. It is believed that this difference is due to the different sex-chromosome constitution known to exist between normal males and females in humans, the male having xy and the female xx constitution.

It has been shown that in most tissues in the human and in a variety of other mammals the sex of the host can be differentiated. Graham (1954) showed that the method could be successfully applied to embryonic tissues of the cat, and Marberger and Nelson (1955) showed that the same was true of human embryonic tissue. The finding of a similar sex difference in amniotic fluid cells (Serr *et al.*, 1955; Dewhurst, 1956; Fuchs and Riis, 1956; James, 1956; Makowski *et al.*, 1956; Shettles, 1956), led to a method for the prenatal diagnosis of foetal sex.

It was concluded, therefore, that by examination of the placenta of a male foetus the origin of a given tissue, whether maternal or foetal could be decided, providing this tissue was composed of cells in the necessary condition for nuclear sexing. A preliminary investigation showed that the placental septum did in fact contain such cells (Sadovsky *et al.*, 1957).

Studies have been made of most of the tissues in the human and some have been found easier to read than others. Skin is by far the easiest, and tumour tissue amongst the most difficult (Lennox, 1956). Nevertheless, most tissues in which a sufficient proportion of cells contain nuclei in the intermitotic phase, can be used for nuclear sexing.

Material and Method

Placentas from 25 normal male foetuses delivered at term, including 2 placentas taken at Caesarean section performed electively, were examined. A control series of 6 placentas from female foetuses were examined, for reasons which will be explained later.

A section of placental tissue in each case was taken which included parts of two adjoining cotyledons, and in which the septum ran through the centre (Fig. 1). In some cases, where possible, the septum itself was also dissected out and examined.

The tissue was immediately fixed in a solution containing formalin 20 parts, 95 per cent alcohol 30 parts, glacial acetic acid 10 parts and distilled water 30 parts (Barr, 1955). After embedding, the sections were cut at 6 μ and stained by the Feulgen method, parallel sections in each case being stained with haematoxylin-eosin.

Results

Examination of the preparations revealed that not all septa were in a similar state of preservation. Some contained far more cells than others interspersed or in clumps amongst a fibrous network with few vessels. Some contained cells which were mostly degenerated, whilst others contained a large proportion of readable cells. In most placentas the sex of the septum was recognizable; Table I comprising the cases included in this series shows the percentages of nuclei showing chromocentres, the counts being made in 23 cases on 100 cells, and in 2 cases on 50 cells, by two independent observers. Figures 1 and 2 (a, b and c) demonstrate a typical case.

In all cases, the percentage of cells showed a female picture. Even though in 3 cases the proportion was under 50 per cent, it was considered due to the poor condition of the septal cells, and regarded as female. In no case was the proportion of chromocentres found to be less than 12 per cent, under which standard it could have been considered as male.

In 4 suitable cases separate counts were made of sections of the septum; a part (A) was chosen deep in the membrane, and another (B) very close to the decidual plate, as demonstrated in

TABLE I

Percentage of Cells with a Chromocentre in the Septa of Placentas from Male Foetuses

Case	At Nuclear Membrane	Not at Nuclear Membrane	Total
1	51	22	73
2	49	26	75
3	51	20	71
4	56	—	73
5	71	2	73
6	49	17	66
7	57	5	62
8	49	26	75
9	58	16	74
10	33	12	45
11	25	2	27
12	49	2	51
13	85	—	85
14	56	1	57
15	62	3	65
16	50	4	54
17	34	1	35
18	55	—	55
19	51	—	51
20	81	1	82
21	79	1	80
22	70	—	70
23	70	4	74
24	60	—	60
25	83	2	85

Figure 3. Results are given in Table II. It will be seen that the proportion of cells containing chromocentres does not show any appreciable difference in the tissue from both areas.

COMMENT

This study seems to show that the placental septa are of maternal origin, and for the main part maternal in composition. The difference in the percentages of counts is accounted for by the varying condition of the septa, which may be due to the general ageing of the placenta towards term. In the cases where the placenta was obtained at an elective Caesarean section performed before term, the septum was clear and the proportion of cells with chromocentres was high.

It is known that in some tissues a lower count is sufficient to determine the origin as female. In various female tissues differences in the proportion of nuclei containing sex chromatin have been found. Ranges vary from 52–85 per cent in skin biopsies (Moore *et al.*, 1953), to 20–64 per cent for buccal mucosa (Moore and Barr, 1955; Marberger *et al.*, 1955; Dixon and Tarr, 1956). Embryonic tissue in the form of amniotic fluid cells showed an analysis range of 34–66 per cent for females, and an average of 12 per cent for males (Sachs *et al.*, 1956). From these observations it is felt that our investigation allows us to conclude the female composition of the tissue examined.

It has been stated that the blood vessels occasionally found in the septa are maternal, but that the cells may be trophoblastic, suggesting as mentioned by Grosser (1927) and Wislocki (1956) an invasion of the tissue by cells of foetal origin. In an attempt to elucidate this point, the septa of female placentas were

TABLE II

Percentage of Cells with a Chromocentre in Different Areas of Septa

Case	Section A			Section B		
	Cells with Chromocentre			Cells with Chromocentre		
	At Nuclear Membrane	Not at Nuclear Membrane	Total	At Nuclear Membrane	Not at Nuclear Membrane	Total
1	70	7	77	66	9	75
2	85	–	85	71	2	73
3	79	1	80	79	3	82
4	72	3	75	83	2	85

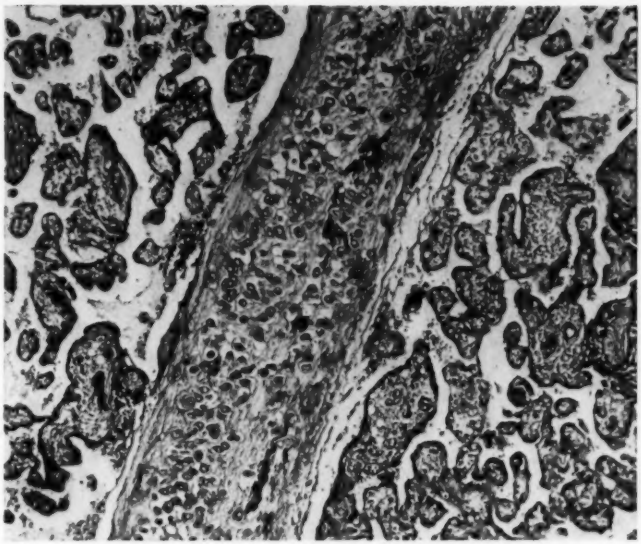
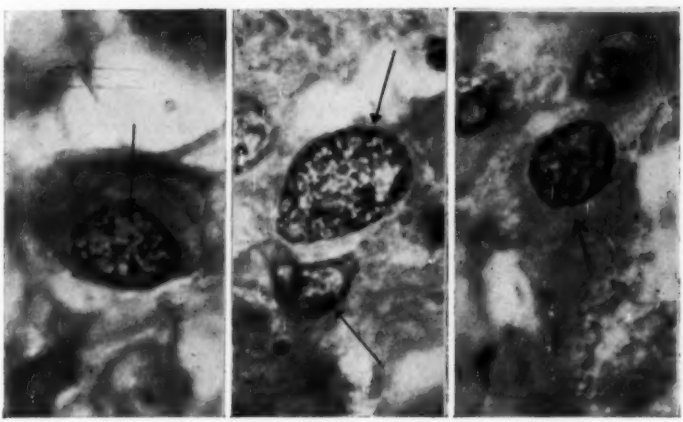


FIG. 1

Photomicrograph of a placental septum. ×80.



(a) (b) (c)

FIG. 2

Photomicrograph of nuclei from placental septal cells, showing sex chromatin bodies. (Feulgen.) ×1,400.

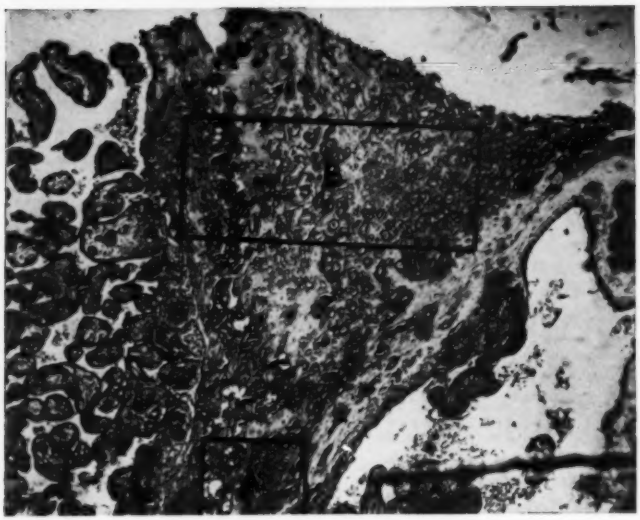


FIG. 3

Photomicrograph of placental septum showing area A deep in the septum, and area B close to the decidual plate, both of which are shown to contain equal proportions of female type nuclei.

examined to see if the percentage of cells showing chromocentres was higher than in the male placentas. Such a finding might have suggested the presence in the septum of foetal cells, which, in the case of the male placenta, would have been demonstrated by a lower percentage of cells containing chromocentres. This was not found to be the case.

Discussing the origin of the placental septum Wislocki (1956) states that he is prepared to accept that the septum was originally decidual, but that this decidual material had been pressed out, as it were, by the trophoblastic invasion from both sides, leaving only a core of maternal cells at the basal end in the early stages of the development of the septum. The results obtained from studies of different areas in the septum, as described (Table II), do not give us cause to believe that the septum contains only a core of maternal tissue near its basal end (Fig. 3, B). Had this been the case, one would not expect to find female type nuclei in the same proportion in these two quite different areas of the septum (Fig. 3, A and B).

Summary

The origin and composition, maternal or foetal, of the placental septum is discussed. By a study based upon nuclear morphological sex differentiation the septum is shown to be composed mainly of female type cells. In different areas of the same septum the findings were similar. These facts are in favour of the view that at term the tissue of the placental septum is maternal both in origin and composition.

This work was supported by a grant from the Hadassah Medical Organization Research Fund.

We are indebted to Prof. B. Zondek for his interest during the course of this study and for facilities provided in his laboratory.

References

Barr, M. L. (1955): *in* Bowes, K. (ed.): *Modern trends in obstetrics and gynaecology*. 2nd series. Butterworth, London. p. 116.

Boyd, J. D. (1956): *Gestation: Transactions of the 2nd Conference*. Josiah Macy, Jr. Foundation, New York. p. 132.

Dewhurst, C. J. (1956): *Lancet*, **1**, 470.

Dixon, A. D., and Tarr, J. B. D. (1956): *Brit. med. J.*, **2**, 799.

Eastman, N. J. (1956): *Williams' Obstetrics*. 11th edition. Appleton-Century-Crofts, New York.

FIAT Review of German Science (1948): *Obstetrics and gynaecology, Part I*. Office of Military Government for Germany, Field Information Agencies Technical. Wiesbaden.

Fuchs, F., and Riis, P. (1956): *Nature (Lond.)*, **177**, 330.

Graham, M. A. (1954): *Anat. Rec.*, **119**, 469.

Greenhill, J. P. (1955): *Obstetrics*. 11th edition. Saunders, Philadelphia. p. 38.

Grosser, O. (1927): *Frühentwicklung, Eihautbildung und Placentation des Menschen und der Säugetiere*. Bergmann, München. p. 373.

James, F. (1956): *Lancet*, **1**, 202.

Latta, J. S., and Beber, C. R. (1957): *Amer. J. Obstet. Gynec.*, **74**, 105.

Lennox, B. (1956): *Scot. med. J.*, **1**, 97.

Makowski, A. L., Prem, K. A., and Kaiser, E. H. (1956): *Science*, **123**, 542.

Marberger, E., Boccabela, R. A., and Nelson, W. O. (1955): *Proc. Soc. exp. Biol., N.Y.*, **89**, 488.

Marberger, E., and Nelson, W. O. (1955): *Brunsbeitr. klin. Chir.*, **190**, 103.

Moore, K. L., and Barr, M. L. (1954): *Acta anat., Basel*, **21**, 197.

Moore, K. L., and Barr, M. L. (1955): *Lancet*, **2**, 57.

Moore, K. L., Graham, M. A., and Barr, M. L. (1953): *Surg. Gynec. Obstet.*, **96**, 641.

Petchenko, A. E. (1956): *Obstetrics*. U.S.S.R. State Publication, Kiev. p. 59.

Ramsay, E. M. (1956): *Gestation: Transactions of the 2nd Conference*. Josiah Macy, Jr. Foundation, New York. p. 229.

Sachs, L. (1954): *Ann. Eugen.*, **18**, 255.

Sachs, L., Serr, D. M., and Danon, M. (1956): *Brit. med. J.*, **2**, 795.

Sadovsky, A., Serr, D. M., and Kohn, G. (1957): *Science*, **126**, 609.

Schroeder, R. (1930): *in* von Möllendorff, W. (ed.): *Handbuch der mikroskopischen Anatomie des Menschen*. VII/1. Springer, Berlin.

Serr, D. M., Sachs, L., and Danon, L. (1955): *Bull. Res. Counc., Israel*, **5B**, 137.

Shettles, L. B. (1956): *Amer. J. Obstet. Gynec.*, **71**, 834.

Spanner, R. (1935): *Morphol. Jahrb.*, **75**, 314.

Stieve, H. (1940): *Z. mikr.-anat. Forsch.*, **48**, 287.

Stieve, H., and von der Heide, I. (1941): *Anat. Anz.*, **92**, 1.

Wislocki, G. B. (1951): *Anat. Rec.*, **109**, 359.

Wislocki, G. B. (1956): *Gestation: Transactions of the 2nd Conference*. Josiah Macy, Jr. Foundation, New York. p. 140.

VOLVULUS COMPLICATING PREGNANCY AND THE PUERPERIUM

BY

ARCHD. L. GOODALL, M.D., F.R.C.S., F.R.F.P.S.
First Assistant Surgeon
Professorial Unit, Royal Infirmary, Glasgow

AND

ALISTAIR W. G. WEIR, M.B., Ch.B.
Late Hall Tutor in Obstetrics and Gynaecology
University of Glasgow

THE occurrence of volvulus of the intestine during pregnancy is an uncommon condition but it has been recognized with increasing frequency recently. It has been estimated that 25 per cent of intestinal obstructions occurring during pregnancy are due to volvulus. The prognosis is related to the stage at which the diagnosis is made; the early cases usually recover whilst the mortality rate rises with delay. The occurrence of three cases in one hospital in a comparatively short period suggests that the lesion is not so uncommon as the absence of case records in the literature suggests.

The first case was recorded by Braun (1885). He wrote of a woman aged 34 years in her 9th pregnancy, her previous children being from 2½–17 years old. She had had one attack described as "eclamptic" at six months and associated with considerable colicky pain and constipation. Three days before admission severe pain had begun and no bowel movement had taken place for 8 days although according to the midwife enemata had produced a motion just before admission. The patient was stout and somewhat livid. The temperature was 99·7° F., the pulse rate 108 per minute and respiration 36 per minute. The uterus was enlarged to a size corresponding to term and distension of the intestine was present, especially in the epigastrium and left hypochondrium. No foetal heart sounds were heard. The urine contained albumin. The danger of further eclamptic fits precluded operation but chloroform was given as a sedative and next day, at 1 p.m., a stillborn male child was born, weighing 3,800 g. The placenta was manually removed. Two days later abdominal pain and dyspnoea increased and she became very thirsty. The following day vomiting began and persisted until her death 24 hours later.

At autopsy, there was gross swelling of the abdomen due to a swollen sigmoid colon. There was splitting of the peritoneal coat at several places. The sigmoid loop was twisted twice on its axis and the afferent loop twisted round its base. Unfortunately, the direction was not stated.

Lambert (1931) in his doctoral thesis collected the records of 29 cases of volvulus of the sigmoid colon during pregnancy and mentioned 16 of volvulus of other parts of the large intestine and 16 of the small intestine. One case was his own, a woman of 41 years in her 6th pregnancy and at term. After three operations the mother recovered but the child died. The mother died two years later of tuberculosis.

Lambert noted that the age distribution was:

20–30 ..	9	40– ..	3
30–40 ..	6		

The number of the pregnancy involved was:

1st ..	1	4th ..	1
2nd ..	7	5th–15th	9
3rd ..	2		

The month of pregnancy at which volvulus occurred was:

3rd	..	1	7th	..	1
4th	..	2	8th	..	3
5th	..	1	9th	..	12
6th	..	6			

The degree of torsion varied from 135°–360°. The direction was mentioned four times, once clockwise and three times counter-clockwise. There were 13 deaths in 29 cases and only 6 live children were produced.

Kohn, Briele and Douglass (1944) reviewed the 79 cases recorded until then and added two episodes in one patient. Cromer and Milstead (1956) collected a further 5 cases making 86 in all; none has been added since. The following 3 cases bring the total recorded to 89.

Some typical case histories have been recorded by White (1914), Bonney and Bridges (1919), Basden (1934), Kornfeld and Daichman (1934), Spence (1937), Rose (1941), Wolfer, Beaton and Anson (1942), O'Meara (1945), Gardiner (1947), James (1950), Moretz and Morton (1950), Murray (1950), Simons (1950), Searle (1951) and O'Malley (1952).

Cases

We have encountered three women with volvulus during the course of pregnancy and the puerperium.

Case 1

Mrs. G.D., a primigravida, aged 34 years, was admitted to Glasgow Royal Infirmary on 16th August, 1950. She was 7-months pregnant. She complained of pain in the hypogastrium of spasmodic type for the previous 24 hours. This was misdiagnosed as the onset of labour and she was admitted to a Maternity Hospital. She was tender over the umbilical area. There had been no bowel movement for four days and nausea and vomiting became severe.

She was shocked and dehydrated on admission, with a dry, furred tongue. The uterus was enlarged to the size of a 7-months pregnancy and there was a mass in the left abdomen which was tympanitic and tender. Bowel sounds were absent.

She was operated upon under spinal anaesthesia. A right paramedian incision was used. A grossly distended, gangrenous pelvic colon about three feet in length was delivered through the wound and resected. The bowel ends were anastomosed and a left colostomy established. Drainage was established through the wound.

The following day the patient went into premature labour and under local anaesthesia was delivered of a small female child with forceps. This child weighed 3½ pounds and survived.

She recovered well and was dismissed on 27th September, 1950. She was admitted again on 8th November for reassessment but no operative treatment was carried out.

On 9th December, 1950, she had further acute colicky pain which lasted 18 hours. There was some nausea and vomiting. The colostomy acted three hours before admission.

She had a further operation on 11th December, 1950, under spinal anaesthesia. There was a volvulus of the caecum, two and a half turns in extent and with early gangrenous patches. This was evidently of some duration. The caecum, terminal ileum and part of the ascending colon were removed and a lateral anastomosis carried out. The abdomen was drained.

She recovered well from this operation and was dismissed on 14th January, 1951. The bowel lumen was re-established and the colostomy closed on 10th August, 1951, under spinal anaesthesia. Since then she has been well.

Case 2

Mrs. J.B., aged 24 years, a primigravida, was admitted to a Maternity Hospital on 26th February, 1952. She was 4-months pregnant and had been diagnosed as "pyelitis". Pain persisted in the right hypochondrium of a colicky nature and vomiting commenced. There was no bowel movement. There had been an appendicectomy nine months previously through a right paramedian incision. This had been complicated by peritonitis and paralytic ileus. She was transferred to a surgical unit on 28th February, 1952, when she was found to be grossly distended and suffering from intestinal obstruction.

On 28th February, she was operated upon under spinal anaesthesia. A right paramedian incision was made and a volvulus of the terminal ileum and ascending colon found. The apex was attached to the old scar by an adhesion. The distal bowel was gangrenous and four feet were resected. A colostomy was established.

On 4th March she delivered a stillborn 4½-month foetus but her condition rapidly deteriorated and she died the following day. No autopsy was performed.

Case 3

Mrs. M.M., aged 28 years, had had 5 children and 2 miscarriages. This patient was referred to the antenatal clinic at the 33rd week of her 8th pregnancy. X-ray examination of the abdomen revealed the presence of triplets. She was, therefore, admitted to hospital. The pregnancy thereafter was uneventful apart from an iron deficiency anaemia which was treated with intramuscular iron.

Labour commenced spontaneously two days past term. After 8 hours in the first stage and 1 hour in the second stage, general anaesthesia was induced. The first child, weighing 6 pounds 6 ounces, was delivered by forceps.

The second child, weighing 5 pounds 12 ounces and the third child, weighing 4 pounds 10 ounces, were delivered by internal version and breech extraction. The third stage was normal.

Puerperium. The patient was very exhausted on the day following delivery. She complained of fairly severe lower abdominal pain some 14 hours after delivery and on examination was found to have a distended bladder. She had been unable to pass urine since delivery. The bladder was catheterized and 42 ounces of clear urine were obtained. The patient's pain was considerably eased following this. The fundus was firm and the lochia normal.

The following day the patient again complained of spasmodic lower abdominal pain. The pain was felt mainly in the left iliac fossa and in the hypogastrium. She did not vomit. On examination she looked pale and tired. Her temperature and pulse were normal and her tongue was moist and clean. The abdomen was slightly distended and was resonant to percussion. The uterus was firm, but was very tender to palpation. There was no dullness in the flanks. Bowel sounds were present and were normal. She stated that she had passed flatus per rectum since delivery; her bowels had not moved.

The following morning the patient's abdomen was very much more distended. She still had not vomited and she had been drinking fairly well. Her urinary output was satisfactory. Her bowels had not moved and no further flatus had been passed. In addition to a very marked abdominal distension, there was generalized tenderness over the whole of the abdomen. High-pitched metallic tinkling bowel sounds were heard on auscultation. A straight X-ray of the abdomen was taken. This showed marked distension of the whole of the large bowel from the caecum down to the pelvic colon. There were multiple fluid levels. The appearances were those of a large bowel obstruction at the level of the pelvic colon.

Operation Notes (21st December, 1956). The abdomen was opened through a left paramedian incision. The large bowel was distended down to and including the pelvic colon. The uterus was the size of a 20-weeks gestation and there was an adhesion between the pelvic colon and a small subserous fibroid which was present at the left uterine cornu. This adhesion was divided between ligatures. On further close inspection, it was found that the pelvic colon was rotated clockwise through 180 degrees. The rotated portion of bowel was congested but its vitality was unimpaired. The bowel was untwisted and a long rectal tube was passed up through the anus to the splenic flexure. The abdomen was then closed in layers. It was thought that the obstruction was probably incomplete. The question of fixing the long pelvic colon was considered but this was thought to be inadvisable on the first occasion of the syndrome.

The patient made an uneventful recovery and the rest of the puerperium was normal. All three babies thrived.

Discussion

Volvulus during pregnancy and the puerperium is possible at any stage but is most commonly found in the third trimester, 50 per cent of the recorded cases occurring then. The most common site is the sigmoid colon (52 per cent), then other parts of the large intestine (24 per cent), then the small intestine (24 per cent). It seems to be rather more common in the older age groups and in multiparae.

The cause of the condition is essentially a congenitally long mesentery of the colon which may be abnormally attached to the posterior abdominal wall; without a long mesentery torsion is impossible. An axis for the torsion may be provided by an inflammatory band (Case 2) or by a congenital anomaly. The effect of diet upon torsion in the non-pregnant woman has been noted for many years, especially in Western India (Andersen, 1956), Africa (Kerr and Kirkaldy-Willis, 1946), and some Eastern European countries. A large or bulky vegetable diet is inculpated. These factors may all be related to the occurrence of the condition in pregnancy. If the developing uterus displaces the intestine sufficiently, the action of peristalsis on a bulky bowel content in a lax bowel will produce or exaggerate torsion. The sudden decrease in size of the uterus on delivery may have the same effect.

The torsion is usually counter-clockwise and varies in degree between 135° and 800°. The signs and symptoms are those of obstruction complicated by the presence of a pregnant or puerperal uterus. The onset of colicky pain and vomiting, at first of gastric contents, later of bile-stained fluid, and later of intestinal contents, should suggest the diagnosis of obstruction. Distension may be early and should be evident even when the uterus is large: plain X-ray films of the abdomen will confirm its presence. There is usually tenderness and guarding over the twisted loop and a mass may be felt. Concealed accidental haemorrhage has to be excluded.

The treatment of volvulus may be conservative or operative. The conservative method is to pass a sigmoidoscope along which a rubber tube is passed to reduce and maintain reduction of the volvulus. This method is only useful in volvulus of the sigmoid colon and is not always successful. The time spent on manipulation might be better spent on laparotomy.

Operative treatment is laparotomy with reduction of the volvulus. If the bowel is viable, a tube passed along its lumen may maintain reduction. If the bowel is not viable, a resection, either in one or two stages, will be necessary. To avoid recurrence, resection of the long loops has been advised. We would not advise this as a primary procedure but, in the presence of recurrence, it is obligatory. The problem of whether to terminate pregnancy requires clinical judgment. In general terms, the pre-viable child should be preserved; the viable child may be delivered by Caesarean section. If resection or exteriorization of the bowel is necessary, termination of pregnancy is probably justified in the interests of the mother.

Summary

(1) The attention of surgeons and obstetricians is drawn to the occurrence of volvulus as a cause of intestinal obstruction during pregnancy. Twenty-five per cent of obstructions in pregnancy are due to this cause.

(2) Three cases of volvulus during pregnancy are recorded.

(3) The usual site is the sigmoid colon, the usual age 21–30, but when the percentage of pregnancies in each age period is considered, there is a higher proportion in the age group 31–40.

(4) Treatment should be by laparotomy and untwisting. Resection should be reserved for the necrotic or recurrent case.

We are grateful to Professor J. A. G. Burton who operated upon Cases 1 and 2 for permission to publish them, to Dr. Hugh Stirling who delivered Case 1 and to Professor Ian Donald for help and encouragement.

References

Andersen, D. A. (1936): *Brit. J. Surg.*, **44**, 132.
Basden, M. M. (1934): *Brit. med. J.*, **1**, 1119.
Bonney, V., and Bridges, E. C. (1919): *Brit. med. J.*, **2**, 846.
Braun, G. (1885): *Wien. med. Wschr.*, **35**, 761.
Cromer, J. K., and Milstead, V. (1956): *Amer. J. Proctol.*, **7**, 238.
Gardiner, R. H. (1947): *Brit. med. J.*, **1**, 83.
James, D. W. (1950): *Brit. med. J.*, **2**, 24.
Kerr, W. G., and Kirkaldy-Willis, W. H. (1946): *Brit. med. J.*, **1**, 799.
Kohn, S. G., Briele, H. A., and Douglass, L. H. (1944): *Amer. J. Obstet. Gynec.*, **48**, 398.
Kornfeld, G., and Diachman, I. (1934): *Amer. J. Obstet. Gynec.*, **27**, 768.
Lambert, A. C. (1931): Thèse, Univ. Paris.
Moretz, W. H., and Morton, J. J. (1950): *Ann. Surg.*, **132**, 899.
Murray, A. G. (1950): *Brit. med. J.*, **2**, 659.
O'Malley, R. D. (1952): *New Engl. J. Med.*, **246**, 744.
O'Meara, D. J. P. (1945): *Brit. med. J.*, **2**, 626.
Rose, I. (1941): *Brit. med. J.*, **2**, 577.
Searle, W. N. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 941.
Simons, P. (1950): *J. Obstet. Gynaec. Brit. Emp.*, **57**, 445.
Spence, J. H. (1937): *Brit. med. J.*, **2**, 1169.
White, C. (1914): *Proc. R. Soc. Med.*, **7**, Sect. Obstet. Gynaec., 305.
Wolfer, J. A., Beaton, L. E., and Anson, B. J. (1942): *Surg. Gynec. Obstet.*, **74**, 882.

EXPERIENCE WITH NEW CONTRAST MEDIA FOR HYSTEROSALPINGOGRAPHY

BY

H. E. REISS, M.A., B.M., B.Ch., M.R.C.O.G.

AND

MARIA E. GROSSMANN, M.D., M.R.C.S., L.R.C.P., D.M.R.E.

From the Obstetric Unit and X-ray Diagnostic Department, University College Hospital, London

SINCE the first injection of a radio-opaque substance into the uterine cavity in 1910, the search for an ideal contrast medium has continued. Rubin (1941) has re-stated the properties of an ideal contrast medium for hysterosalpingography: that it should be adequately opaque, rapidly absorbed, non-irritant, moderately viscous, and capable of being sterilized. Norman (1955) considered that such an ideal had not yet been attained.

Freeth (1952) and Barnett (1955), in recent reviews of the history of various contrast media, have commented upon the disadvantages of oily preparations and the safety of water soluble ones. However, iodized oils, introduced by Sicard and Forrestier in 1922, continue to be widely used in many clinics. Inherent in their use are the following risks:

(1) Retention of lipiodol in the Fallopian tubes was reported by Rubin (1936) in the case of tubes which were the site of permeable strictures. This is due to impaired tubal function and the viscosity of lipiodol. Residues of lipiodol, foreign body giant-cell infiltration and closure of the lumen are the demonstrable pathological changes. In one case Rubin (1939) demonstrated a caseating salpingitis provoked by lipiodol.

(2) Delayed absorption of lipiodol from the peritoneal cavity is well known and has been shown repeatedly by X-ray examinations months and even years after the original examination. Rubin (1936, 1939) has reported the demonstration at subsequent laparotomies of a thin, fatty deposit on the pelvic organs; foreign body reactions with the formation of giant cell systems, multiple cysts, and peri-tubal adhesions are other findings.

(3) Intravasation is the most serious immediate risk of the use of oily media in hysterosalpingography. This subject has previously been reviewed by one of us (Grossmann, 1946) with a description of 2 cases of oil embolism.

(4) A further risk of using lipiodol is the occasional flare-up of a low-grade infection into acute salpingitis and pelvic peritonitis.

Apart from these risks, there are further disadvantages in the use of lipiodol:

(1) In the demonstration of hydrosalpinx, the oily media are most unsatisfactory. Often this condition is missed altogether as a result of the failure of the oily solution to mix with the contents of the distended tube, and its tendency to remain deposited in the most dependent part of the tube. This experience is also recorded by Barnett (1955). Interpretation may be exceptionally difficult in other cases where the lipiodol globulates in the distended tube, simulating peritoneal spill.

This is a matter of great importance to us, as hydrosalpinges on one or both sides were actually demonstrated in 36 of the 200 cases here reported.

(2) Lipiodol is so opaque that it may fail to show the finer details of the mucosal pattern of the uterus and tubes. Furthermore, its viscosity is so great that stenosed and diseased tubes may

fail to fill, and tubal patency in these cases cannot reliably be established. This has been well illustrated by Kjellberg (1942), who repeated examinations with water soluble media in cases previously examined with lipiodol.

Both these disadvantages are of particular significance in relation to the diagnosis of pelvic tuberculosis.

(3) The need for a 24-hour film is inherent in the use of lipiodol which, because of its high viscosity, requires considerable time before free spill occurs. This is inconvenient for patient and radiologist alike.

Water-soluble contrast media, with their rapid and complete absorption, avoid the chief risks enumerated. Intravasation, if it occurs, is free from danger. Their low viscosity permits accurate delineation of the uterine and tubal cavities, reveals minute details of their mucosal pattern, and ensures quick spill which enables rapid diagnoses to be made, with saving in time and irradiation. Furthermore, these media mingle readily and completely with the contents of a hydrosalpinx. Bligh (1955) describes the following criterion for the accurate diagnosis of hydrosalpinx: the persistence of pockets of contrast medium 1 to 2 hours after the original injection. Any contrast medium retained in the uterus will have flowed back into the vagina by this time, whilst freely spilled fluid will have been completely absorbed from the peritoneal surface. The pockets seen on the late films are therefore contrast medium, diffused through the contents of a diseased tube from which absorption is delayed (Figs. 1 and 2).

However, the unduly low viscosity of water-soluble contrast media may have one great disadvantage: as Rubin and Morse (1939) pointed out, the crystalline iodine compounds used in excretory urography pass through the tubes so quickly that the latter are hardly outlined and are rapidly overshadowed by the spill into the peritoneal cavity.

For this reason various thickening agents have been added, such as carboxy-methyl-cellulose (CMC) (Roland *et al.*, 1953), poly-vinylpyrrolidone (PVP) (Rubin *et al.*, 1953), and dextran (Norman, 1955).

Unfortunately, disturbing reports on some of these thickening agents have recently appeared. Bergman *et al.* (1955) reported granuloma formation in the pelvic peritoneum in 16 out of 18 cases where CMC had been used. Kantor, Kamholz and Smith (1956) report a case investigated with Salpix (PVP) in which, at subsequent laparotomy 9 months later, the omentum, intestines and pelvic organs were studded with grey-white implants, similar to tubercles. The Fallopian tubes were red and swollen. Tuberculosis was diagnosed and a total hysterectomy with bilateral salpingo-oöphorectomy was performed. Pathological examination revealed multiple granulomata all at the same stage of development, with no caseation. Examination with polarized light revealed doubly refractile foreign body material, similar to Salpix.

The safety of PVP depends to some extent on the size of the molecule used. Permanent storage in the liver and reticulo-endothelial system, after its use as a plasma substitute, has been described by Boyd, Fletcher and Ratcliffe (1953) and by Altemeier *et al.* (1954). Admittedly, in these cases, PVP was used in enormous doses compared with the small amounts injected in hysterosalpingography. More recently, there have been as yet unconfirmed reports of sarcomatous changes in the lymphoid system of rats experimentally subjected to intraperitoneal injection of large amounts of PVP. These changes could not be reproduced in mice.

In order to avoid these possible risks, clinicians in this country have recently tried out media of adequate viscosity, but in which the viscosity depends on the size of the molecule and not on any supplementary thickening agent.

Present Series

On 1st January, 1956, we discontinued the use of PVP-containing contrast media, and started an investigation into the suitability of "Uriodone 35", Endografin Schering, and Biligrafin 50 per cent Schering, for hysterosalpingography.

"Uriodone 35" is a preparation of 3-5-di-iodo-4-pyridone-N-acetic acid and diethanolamine, containing approximately 50 per cent iodine, and identical with injection of Diodone B.P. 35 per cent. This substance, prepared for intravenous injection for excretory urography, was used by

us in only 8 cases; it was discarded on account of its low viscosity and poor radio-opacity. Visualization of the tubes was only fleeting: too great and immediate a peritoneal spill gave a confusing picture, obscuring uterus and tubes; hydrosalpinx was too difficult to diagnose from peritoneal spill, necessitating too many ½-hour films; and too rapid outlining of the bladder, resulting from speedy absorption from the peritoneum, obscured even the ½-hour films.

This experience was similar to that of Rubin and Morse (1939) in their experimental study of various contrast media in the Macaque monkey.

At about this time (February, 1956) it was suggested to us to try Endografin and Biligrafin produced by Schering, A. G., Berlin. These are chemically identical substances, each containing the methyl glucaminate of N,N′-adipic-di-(3-amino-2,4,6-triiodobenzoic acid), but their contrast intensity and viscosity differ (Table I). Neither contains supplementary thickening agents, so that the viscosity depends entirely on the size of the molecule and the concentration.

TABLE I

	Per cent	Centipoises
Viscosity at 37° C.:		
Endografin	70	18
Biligrafin	50	6
Urografin	76	7·3
Urografin	60	4·15

Using Endografin 70 per cent we examined 23 cases, but discontinued its use as we found its viscosity too high and its radio-opacity too intense, so that the mucosal pattern of the uterus, tubes and cervical glands was at times obscured. Furthermore, pain, of a delayed onset —about 1 to 3 hours after the injection—was a frequent complaint.

Biligrafin was used in the next 16 cases. This substance was originally developed as an intravenous biliary contrast agent. Contrast in hysterosalpingography was unsatisfactory with the 30 per cent solution. This was easily remedied by the use of a 50 per cent solution, but this produced severe peritoneal irritation. Nearly every patient complained of pain which was maximal from 1 to 3 hours after the examination. The viscosity of Biligrafin was also considered to be somewhat low, resulting in poor visualization of the tubes and too rapid spill in some cases. We found that an unduly large number of exposures was used in each case, though this disadvantage would not be encountered to the same extent by those who use screening as part of their technique.

We next tested Urografin, another of the triiodated contrast agents newly developed by Schering, A. G., Berlin. It is available in two concentrations, Urografin 76 per cent and Urografin 60 per cent, and each consists of an aqueous solution of a mixture of the sodium and methyl-glucamine salts of N,N′-diacetyl-3, 5-diamino-2,4,6-triiodo-benzoic acid.

Urografin is the least toxic of all the existing iodine-containing contrast media (intravenous M.L.D. for the rat=14·7 g. per kg. body weight). It is excreted in the urine with extraordinary rapidity. It was developed, and has been used extensively, for intravenous urography, aortography, and angiography of the heart and brain. Doses up to 50 ml. intravenously and 60 ml. intra-arterially have been used safely. Its use in hysterosalpingography has not been previously described, and was suggested to us by Dr. Cochrane Shanks.

In the first 5 cases, we used the weaker, less viscous preparation, Urografin 60 per cent. Not satisfied with contrast and confused by too rapid spill, we turned to Urografin 76 per cent. This has been used in our department routinely since May, 1956, in a total of 148 cases.

TECHNIQUE

The examination is carried out as far as possible 10 to 14 days after the onset of the last period: this avoids the possible risks of intravasation from too early an injection, or of disturbing an early pregnancy by too late an injection.

The examination is explained to the patient when the appointment is made. She attends the gynaecological ward at 11 a.m. on the appointed day, where she is provided with a theatre gown and dressing gown, and rested on a couch. One hour before the examination, Pethidine 100 mg. is given intramuscularly and tablets Seconal (Quinalbarbitonum sodium) gr. iii (200 mg.) by mouth.

FIG. 1
Bilateral distal sealed hydrosalpinx.

FIG. 2
Same patient, 45 minutes after injection of Urografin 76 per cent: uterus now empty; contrast medium persists in the hydrosalpinges. No peritoneal spill.

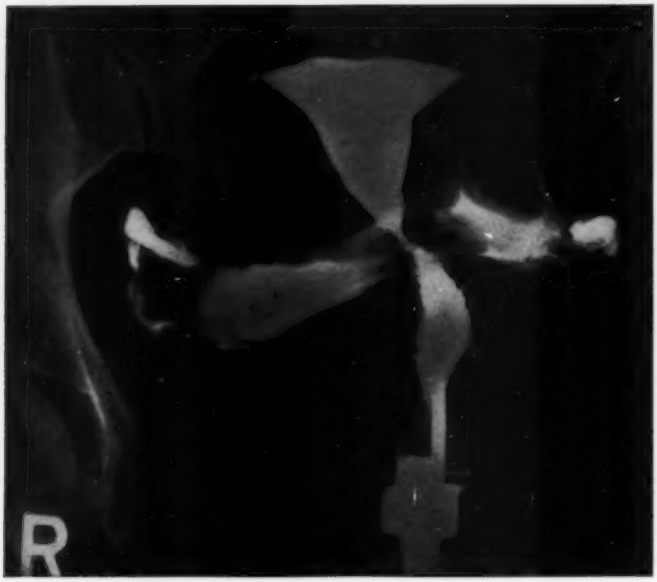


FIG. 3

Normal hysterosalpingogram. Note fine detail of cervical canal. Immediate peritoneal spill has occurred.

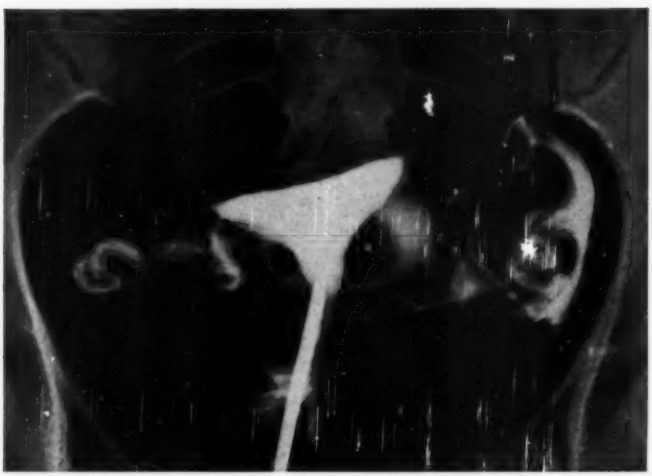


FIG. 4

Normal hysterosalpingogram, with tubal patency. Note longitudinal folds in ampullary ends of tubes.

FIG. 5

Intravasation of Urografin 76 per cent. Contrast medium seen in vessels of uterine wall, as well as uterine and ovarian veins.

FIG. 6

A case of proved endometrial tuberculosis. Irregular contour of uterine cavity; wide tubes with dilated ampullary ends; no peritoneal spill.

Just before the examination, the patient is instructed to empty her bladder, and is then wheeled to the X-ray department where she is placed on the examination table in the lithotomy position. Following a vaginal examination to ascertain the position of the uterus, a Sims's speculum is introduced, and the cervix and vagina are cleansed. The cervix is then grasped with a volsellum forceps and a sound introduced to test the patency of the cervical canal, the tone of the internal os sphincter, and the length of the uterus. A cannula with a rubber olive, attached to an ordinary 20 ml. syringe filled with warm contrast medium, is then introduced into the cervical canal, and a good seal ensured by counter-traction on the volsellum. The Sims's speculum is then removed.

The patient is now released from the lithotomy position and arranged on the table. Four to 5 ml. of contrast medium are injected and the first exposure made immediately. Whilst awaiting the wet film, pressure on the cannula is maintained, so that any tubal spasm which may be present is overcome during the next 3 to 4 minutes. Subsequent films are taken as necessary, in accordance with the information obtained from the first film; oblique, lateral and stereoscopic views are taken when required, and more contrast medium may have to be injected.

In the majority of cases 1 or 2 exposures suffice to reach an accurate diagnosis. In cases of doubtful tubal patency or apparent hydrosalpinx, a final film is exposed 30 minutes after the last injection.

Finally, the patient is wheeled back to the ward where she is allowed to sleep off the sedation before going home.

Radiographic details. An over-couch tube with a small cone to reduce scatter is used. The anode-film distance is 36 inches. A Potter-Bucky diaphragm is used and the exposure is 0·8 seconds, with 200 M.A. at 69 K.V.s. Protection for the gynaecologist's hands is given by a lead screen.

Results

We have re-examined the 200 hysterosalpingograms in this series and believe that in Urografin 76 per cent, used in the last 148 of these cases, we have found the most satisfactory contrast medium at present available. It is safe, mixes well with body secretions and the contents of hydrosalpinges (Fig. 1), and gives satisfactory contrast without obscuring fine details (Figs. 3 and 4). It is completely absorbed in a short time and in the majority of cases 2 films are adequate for diagnostic purposes. Intravasation (Fig. 5) is devoid of risk, and screening not necessary to guard against this complication.

Pain in hysterosalpingography may be due to the associated instrumentation, the distension of the uterus or tubes, or the peritoneal spill. With only little experience it is possible to distinguish between these and generally to avoid pain due to errors in technique. Using Urografin 76 per cent we have encountered severe pain due to peritoneal irritation in only one case, and moderate pain on only two occasions. There have been no other objective or subjective ill-effects in this series. A flare-up of chronic pelvic infection has not occurred in this series, although the examination was carried out in several unsuspected and 2 known cases of proved pelvic tuberculosis (Fig. 6).

Discussion

Biligrafin 50 per cent was used by MacGregor and Sheach (1956) with satisfactory results in 51 cases. Sandler (1956) reported moderate to severe peritoneal irritation in 13 out of 16 cases. A similar experience was recorded by O'Driscoll (1956). These symptoms did not manifest themselves until several hours after the examination. We noted similar symptoms in our patients after they had recovered from their pethidine-seconal analgesia. MacGregor and Sheach's patients went home immediately after the examination (personal communication), and it would appear that peritoneal irritation is noted only if the patients are kept under observation for some hours after the examination, or are asked about their experience at the next attendance.

Endografin has been used by Menzies (1956) and McCann and Menzies (1957) with apparently satisfactory results; however, Davies, Fisher and Rocker (1957) report marked lower abdominal pain, due to peritoneal irritation, in 11 of their 75 cases, and our experience is similar.

As far as our technique is concerned, a Leech-Wilkinson cannula, general anaesthesia and screening are not used. We agree with White (1951) that the Leech-Wilkinson cannula may tear the cervix, and by causing pain may lead to tubal spasm. Furthermore, the cervix is no rigid structure and its normal appearance may be grossly distorted by the introduction of this type of cannula. This is of particular importance in the diagnosis of incompetence of the internal cervical os.

Tubal spasm is one of the major pitfalls of hysterosalpingography and, as Stallworthy (1948) and White (1951) have pointed out, emotional distress associated with general anaesthesia may even perpetuate the spasm. We prefer to rely on reassurance and explanation at all stages, admission and sedation, gentleness, and the use of a warm solution during injection. Cornual block is a rare finding in our series.

Screening, as an essential part of hysterosalpingography, is still practised by Stallworthy (1955), Barnett (1955), and McCann and Menzies (1957). Preiskel and Pollock (1952) and Osborn (1952) hold that screening involves excessive and unnecessary irradiation to the ovaries, but MacGregor and Oliver (1952) have shown that screening for short times with due precautions for patient and operator need not cause excessive irradiation. We feel, with Pollock and Preiskel (1951), that better films are obtained by the use of an overhead tube and Potter-Bucky diaphragm, than with the under-couch tube needed for screening, and agree with Rubin (1955) that failure to screen seldom causes diagnostic difficulties to the experienced clinician. Furthermore, there is the distinct possibility that less experienced clinicians may screen for much longer periods of time than those advocated by MacGregor and Oliver.

Conclusion

Most of the 200 cases in this series were referred for hysterosalpingography from the fertility clinic of University College Hospital on account of primary or secondary infertility or repeated abortions. As the clinical results of this investigation depend entirely on the selection of cases, there is little point in presenting a detailed analysis of our results in a paper dealing with technique of examination and choice of contrast medium.

Urografin 76 per cent is now used by us routinely, as the least harmful and most satisfactory contrast medium at present available. Our methods have proved entirely satisfactory provided radiologist and gynaecologist cooperate closely during the examination, are both familiar with the clinical aspects of each case, know exactly what they wish to demonstrate by their examination, and vary their technique accordingly.

Acknowledgments

We wish to thank Dr. S. Cochrane Shanks, Professor W. C. W. Nixon, and Dr. G. I. M. Swyer for permission to publish our findings and for their help in the preparation of this paper; Sister Quirke and her staff of the X-ray Diagnostic Department for their close cooperation; and the British representatives of Schering A. G., Berlin, for their assistance and the provision of samples of Urografin 76 per cent.

References

Altemeier, W. A., Schiff, L., Gall, E. A., Giuseffi, J., Freiman, D., Mindrum, G., and Braunstein, H. (1954): *Arch. Surg.*, **69**, 309.
Barnett, E. (1955): *J. Fac. Radiol.*, **7**, 115.
Bergman, F., Gorton, G., Norman, C., and Sjöstedt, S. (1955): *Acta radiol., Stockh.*, **43**, 17.
Bligh, A. S. (1955): *Brit. J. Radiol.*, N.S., **28**, 30.
Boyd, A. M., Fletcher, F., and Ratcliffe, A. H. (1953): *Lancet*, **1**, 59.
Davies, D. K. L., Fisher, H. J., and Rocker, I. (1957): *Brit. med. J.*, **2**, 859.
Freeth, D. (1952): *Lancet*, **1**, 15.
Grossmann, M. E. (1946): *Brit. J. Radiol.*, N.S., **19**, 178.
Kantor, H. I., Kamholz, J. H., and Smith, A. L. (1956): *Obstet. Gynec.*, **7**, 171.
Kjellberg, S. R. (1942): *Acta radiol., Stockh.*, Suppl. 43.
McCann, P., and Menzies, D. N. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 416.
MacGregor, W. G., and Oliver, R. (1952): *Lancet*, **2**, 563.
MacGregor, W. G., and Sheach, J. M. (1956): *Lancet*, **2**, 682.
Menzies, D. N. (1956): *Lancet*, **2**, 785.
Norman, O. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 816.
O'Driscoll, D. T. (1956): *Lancet*, **2**, 993.
Osborn, S. B. (1952): *Lancet*, **1**, 671.

Pollock, M., and Preiskel, E. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 421.
Preiskel, E., and Pollock, M. (1952): *Lancet*, **1**, 374.
Roland, M., Carpenter, F., and Rich, J. (1953): *Amer. J. Obstet. Gynec.*, **65**, 81.
Rubin, I. C. (1936): *N.Y. St. J. Med.*, **36**, 1.
Rubin, I. C. (1939): *Radiology*, **33**, 350.
Rubin, I. C. (1941): *J. Mt Sinai Hosp.*, **7**, 479.
Rubin, I. C. (1955): *J. Obstet. Gynaec. Brit. Emp.*, **62**, 818.
Rubin, I. C., and Morse, A. H. (1939): *Amer. J. Roentgenol.*, **41**, 527.
Rubin, I. C., Myller, E., and Hartman, C. G. (1953): *Fertil. Steril.*, **4**, 357.
Sandler, B. (1956): *Lancet*, **2**, 896.
Sicard, J. A., and Forrestier, J. (1922): *Bull. Soc. méd. Hôp. Paris*, **46**, 463.
Stallworthy, J. (1948): *J. Obstet. Gynaec. Brit. Emp.*, **55**, 171.
Stallworthy, J. (1955): *in* Bourne, A. (ed.): *British obstetric and gynaecological practice. Gynaecology*. Heinemann, London. Chapter 19, p. 661.
White, M. M. (1951): *J. Obstet. Gynaec. Brit. Emp.*, **58**, 573.

A CASE OF PLACENTA PRAEVIA PERCRETA WITH ADDITIONAL UNUSUAL FEATURES

BY

MICHAEL SOLOMONS, M.B., M.R.C.P.I., M.R.C.O.G.
Assistant Gynaecologist
Mercer's Hospital, Dublin

THE existence of placenta accreta as a rare cause of difficulty in the third stage of labour has been recognized for many years. It can be defined as an abnormal penetration by the placenta into the underlying myometrium. In all cases deficiency or absence of the intervening basal decidua is a specific microscopic feature, and invasion of the myometrium by placental tissue can be seen. The normal mechanism of placental separation consequently cannot occur.

CLASSIFICATION

Two classifications have been described by Aaberg and Reid (1945):

(1) (*a*) Total, involving the entire placenta. (*b*) Partial, involving one or more cotyledons. (*c*) Focal, involving part of a single cotyledon.

(2) (*a*) Accreta, where myometrial invasion is of slight degree. (*b*) Increta, when depth of myometrial involvement is greater but is still insufficient to cause perforation. (*c*) Percreta, when placental tissue extends through the entire thickness of the uterine wall and perforation occurs.

HISTORICAL

The clinical condition was first described by Plater in the 16th century, but the histological studies of Langhans (1875) and Berry Hart (1889) were necessary before a description of the underlying pathology became available.

While certain cases of placenta accreta must have escaped publication since Ahlfeld's report of the first histologically proven case in 1889, Irving and Hertig noted only 86 cases in the literature up to 1937 and added 18 of their own. By 1957 Rotton and Friedman found that this total had increased to 240, while Kistner considers that the incidence would be still higher if all placentas, associated with a difficult manual removal, were submitted for histological examination. Placenta praevia accreta is still rarer. Irving and Hertig (1937) reported a total of 14 cases while Kistner, Hertig and Reid (1952), in a most comprehensive article, reviewed a further 11 and added 9 of their own. Case reports in British literature include those of Jackson (1943), Shotton and Taylor (1944), Gemmell (1947), and Chisholm (1948).

The case to be described is one of placenta praevia percreta. This combination appears to be extremely rare. Bakanow's case (1928) is the only one recorded to date, Kistner *et al.* (1952) describing their own Case 5 as "questionable" percreta. The present case has some additional unusual features.

CASE HISTORY

Mrs. T.C., age 35, of Scandinavian origin, visited me during her 8th pregnancy for the first time on 5th March, 1957, when about 37-weeks pregnant. She had been under my care since 1950 and presented the following obstetrical history:

1st pregnancy, 1948—miscarriage at 20 weeks.
2nd pregnancy, 1948—miscarriage at 8 weeks.
3rd pregnancy, 1950—miscarriage at 24 weeks.
4th pregnancy, 1951—spontaneous delivery at 32 weeks. Neonatal death at 2 weeks.
5th pregnancy, 1952—miscarriage at 26 weeks.
6th pregnancy, 1953—miscarriage at 22 weeks.
7th pregnancy, 1955—low forceps delivery after premature labour at 35 weeks; 4¼ pounds, alive.

FIG. 1
Uterus, para-sagittal section. Ectopic placental tissue is shown at A.

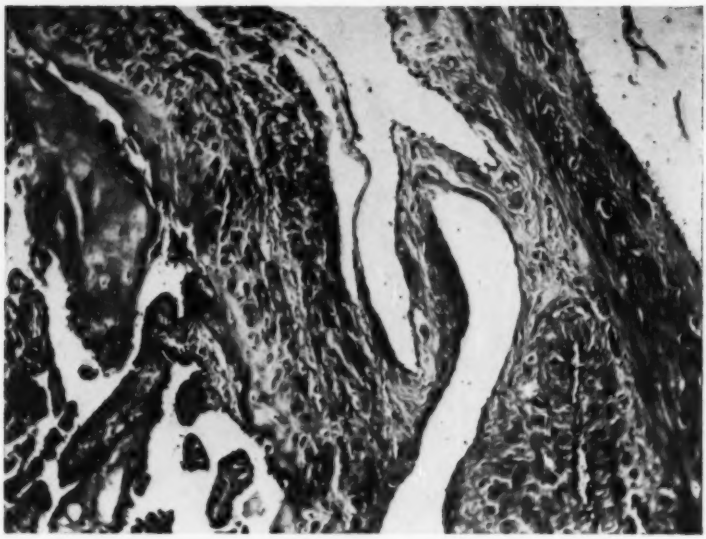


FIG. 2

Placental tissue invading uterine wall to within less than a millimetre of the serous coat shown on the right. ×90.

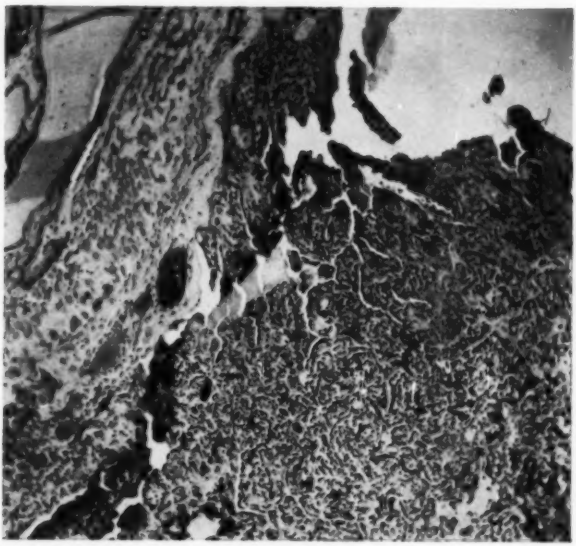


FIG. 3

Ectopic chorionic villi from site A, Fig 1. The villi are seen invading the cervix from without. Dilated cervical glands can be seen top left. ×84.

No medical or gynaecological abnormality was noted when she was first seen in 1950, during the 3rd pregnancy. The previous history was irrelevant. Her blood was group A Rhesus positive, Wassermann and Kahn negative. The blood pressure and urine were normal.

A selection of anti-abortion therapy was employed without success during the 3rd, 4th, 5th and 6th pregnancies, and included the administration of oral iron, calcium and vitamins, progesterone by injection and implantation, and bismuth by injection; as well as rest in bed and general care.

After the fifth failure, hysterosalpingography was carried out in the hope of detecting a congenital uterine abnormality. The film showed "a small filling defect at the left cornu but no other abnormality". Before this could be further investigated the 6th pregnancy began, and ended at 22 weeks.

Shortly after this further disappointment, during a discussion with the patient's husband concerning possible causes of miscarriage, he stated that he had contracted syphilis premaritally during the war years. He then received routine treatment and had been pronounced cured. The following serological tests were carried out as a result of this conversation: Wassermann and Kahn negative, Rhesus negative. Nevertheless, a course of penicillin and bisoxyl by injection and potassium iodide by mouth were prescribed before another pregnancy was considered. This treatment was completed in October, 1953.

As the findings at hysterosalpingography suggested the possibility of a submucous cornual polyp, curettage was performed in September, 1953. No polyp was recovered but irregularity and thinning of the uterine wall were noted in this area.

The patient was advised to defer conception for at least six months. Her local doctor was asked to give her penicillin—in the belief that the husband's history might be a contributory factor—and progesterone as soon as pregnancy could be diagnosed. In March, 1955, she wrote after 7-weeks amenorrhoea, enclosing an early morning sample of urine. A Hogben test proved positive. Her local doctor then began a course of 15 daily injections of 900,000 units of procaine penicillin and thrice weekly injections of 25 mg. progesterone. Calcium, iron and vitamins were taken by mouth. Despite slight vaginal loss with pains when 10-weeks pregnant, following which she stayed in bed for 6 weeks, she progressed satisfactorily and travelled to Dublin when 34 weeks pregnant to await the onset of labour. This began within a week and a 4½ pounds baby was delivered following prophylactic episiotomy. No placental abnormality was found.

The patient's 8th pregnancy terminated the reproductive period of her life. In August, 1956, she wrote following a period of 6-weeks amenorrhoea, asking for advice. The same treatment was prescribed and followed as on the previous pregnancy. Apart from slight vaginal bleeding when 10-weeks pregnant, her doctor reported normal progress throughout. She was advised to come to Dublin at the 34th week and await labour but, owing to various domestic difficulties, did not reach the city until the 3rd March, 1957, three weeks before the estimated date of delivery. I saw her for the first time during this pregnancy on the next day, when the lie was oblique, the head being to the left of the pelvic brim. It could be pushed into the mid-line but would not remain in this position. No other abnormality was noted.

Suspecting the possibility of placenta praevia, as other causes of such a foetal lie seemed unlikely, she was warned not to leave the city, to notify immediately the occurrence of any bleeding, and asked to return for further examination a week later. On the 11th March abdominal palpation showed persistence of the oblique lie. Placentography was carried out next day, the radiologist, Dr. S. J. Boland, reporting "the appearances are highly suggestive of placenta praevia, the placenta is mainly posterior".

In view of the combination of the oblique lie, a highly suggestive placentography and the history of many unsuccessful pregnancies, arrangements were made for elective Caesarean section the next day.

With suitable cross-matched blood available for transfusion and under thiopentone, nitrous oxide, oxygen and cyclopropane anaesthesia, the lower segment operation was carried out without preliminary vaginal examination on the 15th March, 1957.

This proved straightforward until incision of the lower segment encountered part of the placenta lying on the anterior uterine wall. Perforating the placenta digitally the baby's foot was grasped and the child extracted easily as a breech; slow to breathe at first, it soon responded to routine resuscitatory measures.

Ergometrine 0·25 mg. had been given intravenously and separation of the placenta was awaited while the lateral angles of the uterine incision were secured by stay sutures. As these were being inserted abnormal tissue was seen on the extraperitoneal surface of the anterior uterine wall below the incision line (Fig. 1). This seemed so unusual that further inspection of the external surface of the uterus was considered advisable. To facilitate this the uterus was elevated into the abdominal wound. Low on the posterior wall a perforation could now be seen, through which part of the placenta was extruding. The likelihood of a placenta percreta was considered while subsequent examination of the placental attachment confirmed the radiologist's opinion that a major degree of praevia existed, the placenta covering the internal os and extending upwards along both anterior and posterior walls of the lower segment. Here it was abnormally adherent and an attempt to find a line of cleavage was unsuccessful.

As excessive blood loss followed this attempt, transfusion was commenced and the uterine cavity packed with a large wipe. The combination of haemorrhage, irremovable placenta accreta and perforation of the uterine wall, indicated the need for hysterectomy. The total operation was carried out especially in order to effect removal of the extraperitoneal tissue, whose nature was uncertain and which could not be separated completely from the underlying anterior cervical wall. Both ovaries were conserved. Further blood loss was average, satisfactory haemostasis effected, and the abdomen closed in the usual manner.

Prophylactic penicillin was given and the patient allowed out of bed from the 2nd day following operation. Convalescence was normal, the baby of 7 pounds was artificially fed, and both went home well on the 14th day. Vaginal examination before discharge showed some thickening above the vaginal vault but no other abnormality.

At postnatal examination on the 14th May, 1957, the abdominal and vaginal vault incisions were well healed, the vaginal thickening noted earlier having disappeared. A specimen of urine sent at this time for Hogben test was reported negative, while the baby was thriving.

Pathologist's Report

Macroscopic Appearances

The uterus shows the physiological enlargement associated with its post-partum state. A considerable part of the placenta is still *in situ* and fills the uterine cavity to which it is not attached. Firm attachment of the placenta to the myometrium in the lower uterine segment is apparent and the placenta has invaded the uterine wall, causing thinning of the wall leading to rupture in the right postero-lateral region. From the point of rupture the placenta has invaded the extra-uterine tissues and extends forwards to the anterior aspect of the cervix where it has proliferated to produce a mass of ectopic placental tissue which adheres to the anterior aspect of the cervix low down (Fig. 1).

Microscopic Appearances

The uterus, close to the point of rupture, shows invasion of the uterine wall by chorionic villi to within a distance of 0·75 mm. of the serous coat (Fig. 2), the uterine wall being greatly thinned in this region. The placental tissue present outside the uterus and attached to the anterior aspect of the cervix is shown in Figure 3. It is seen to be invading the cervical wall from without, and in the illustration it can be seen approaching the cervical glands on the left of the picture. In this extra-uterine extension of the placenta the chorionic villi are smaller than normal and are closely huddled together.

The muscle fibres of the body and cervix show enlargement in proximity to the chorionic villi, providing the appearance of decidua. This reaction was noticed at numerous points in the myometrium where it was being invaded by the villi. It is well seen in Figure 2.

Comment

It is considered that the curettage carried out in September, 1953, the treatment of the husband, and the prenatal administration of penicillin during the 7th and 8th pregnancies were the main therapeutic measures responsible for the successful conclusion to these pregnancies.

Summary

(1) A case of partial placenta percreta is described, complicating a major degree of placenta praevia.

(2) The rarity of this combination is stressed.

(3) Additional unusual features included the finding of part of the placenta in an extra-peritoneal position at the time of operation; and a series of previously unsuccessful pregnancies probably attributable in part to the husband.

(4) Treatment by Caesarean hysterectomy resulted in a live mother and child.

Acknowledgments

I wish to thank Professor R. A. Q. O'Meara, School of Pathology, Trinity College, Dublin, for his valued report on the specimen; and Mr. F. Murray for providing the photographs.

References

Aaberg, M. E., and Reid, D. E. (1945): *Amer. J. Obstet. Gynec.*, **49**, 368.
Ahlfeld, F. (1889): *Z. Geburtsh. Gynäk.*, **16**, 302.
Bakanow, —. (1928): *Zbl. Gynäk.*, **52**, 2159.
Chisholm, W. N. (1948): *J. Obstet. Gynaec. Brit. Emp.*, **55**, 470.
Gemmell, A. A. (1947): *J. Obstet. Gynaec. Brit. Emp.*, **54**, 213.
Hart, D. B. (1889): *Edinb. med. J.*, **34**, 816.
Irving, F. C., and Hertig, A. T. (1937): *Surg. Gynec. Obstet.*, **64**, 178.
Jackson, I. (1943): *Proc. R. Soc. Med.*, **36**, 362.
Kistner, R. W., Hertig, A. T., and Reid, D. E. (1952): *Surg. Gynec. Obstet.*, **94**, 141.
Langhans, T. (1875): *Arch. Gynäk.*, **8**, 287.
Plater, F. Quoted by Irving and Hertig (1937).
Rotton, W. N., and Friedman, E. A. (1957): *Obstet. Gynec.*, **9**, 580.
Shotton, D. M., and Taylor, C. W. (1944): *J. Obstet. Gynaec. Brit. Emp.*, **51**, 340.

STUDIES OF THE OXYGEN CONSUMPTION OF FRESH PLACENTAL TISSUE FROM NORMAL AND ABNORMAL PREGNANCIES

BY

RACHEL B. MACKAY, M.D.

From the Clinical Laboratories of the Simpson Memorial Maternity Pavilion of the Royal Infirmary, Edinburgh, and the Department of Obstetrics and Gynaecology, University of Edinburgh

FOR many years it has been known that placental changes are closely associated with pre-eclampsia. Although opinions have varied as to which is the primary disturbance, it is widely accepted at present that in patients suffering from pre-eclampsia there is a degree of placental ischaemia, which accelerates the normal process of ageing. This ischaemia, as well as being reflected in histological (Tenney and Parker, 1940) and histochemical changes (Wislocki and Dempsey, 1946), might also be associated with a change in the aerobic metabolism of the tissue.

Although the results of several studies of the rate of oxygen consumption of placental tissue have been published during the last thirty years, from the early German investigations (e.g., Rech, 1924), using perfusion methods of estimation, to the more recent experiments of Page (1948), Hellman, Harris and Andrews (1950) and Villee (1953), only the more recent studies have included particular reference to the effects, if any, of pre-eclampsia. Relatively few cases have been investigated, and whereas Hellman, Harris and Andrews, and Villee showed no significant change from normal levels in severe, acute pre-eclampsia, Page observed a lower rate of oxygen consumption in cases of severe pre-eclampsia in which evidence of this complication had existed for some weeks.

In this investigation we have made an endeavour to clarify these findings by studying a larger number of cases, not only of severe, acute pre-eclampsia, but also of less severe pre-eclampsia in which signs or symptoms had existed for some time.

As relatively little data was available regarding the effect of other complications, such as essential hypertension and diabetes mellitus, on the rate of oxygen consumption of placental tissue, it was decided to extend this study to include a number of pregnancies with these complications. In addition, a number of twin pregnancies were investigated.

As a basis for comparison of the results obtained in these cases, a group of clinically normal cases was studied to form a pattern for normal pregnancy. In this group particular attention was given to pregnancies which had continued beyond the expected date of delivery.

METHODS

The placentae were collected immediately after delivery. In most instances the experiment was carried out at once but in the few cases where this was impossible the specimens were stored in a refrigerator for a few hours. Experiments showed that storage up to 8 hours did not affect the rate of oxygen consumption provided that the specimens were placed in the refrigerator immediately following delivery.

Four samples were taken from the whole thickness of the tissue, excluding the chorionic and decidual surfaces. Areas of gross degeneration were excluded. The samples were dissected free from larger blood vessels, washed in Krebs-Ringer phosphate solution, dried with filter paper, finely minced and mixed. A weighed amount of tissue (150–170 mg.) was added to 3 standard Warburg flasks containing Krebs-Ringer phosphate solution, with 0·2 per cent

glucose, at pH 7·4. A similar quantity of tissue was dried overnight at 105° centigrade and re-weighed.

Oxygen consumption was measured in the Warburg apparatus at a constant temperature of 37·6° centigrade in an atmosphere of room air, carbon dioxide being absorbed by 0·2 ml. of 20 per cent potassium hydroxide in the central well of the flask. Readings were taken every 30 minutes for a period of 1½ hours after equilibration. The results obtained in the 3 flasks showed close agreement (always well within 0·1 Qo_2).

The results are expressed as Qo_2–oxygen uptake in microlitres per milligram dry weight of tissue per hour.

Material

The oxygen consumption of the placental tissue was studied in a total of 267 patients; 148 with clinically normal pregnancies, 74 with pregnancies complicated by pre-eclampsia or eclampsia, 15 with essential hypertension, 4 with essential hypertension and superimposed pre-eclampsia, 10 with diabetes mellitus and 16 with twin pregnancies.

Normal Pregnancy

The 148 clinically normal patients were delivered at various periods of gestation; 8 (9–27 weeks), 11 (28–35 weeks), 19 (36–38 weeks), 60 (39–41 weeks) and 50 (42–43 weeks) (see Table I). All of these patients had a blood pressure recording of less than 140/90 throughout pregnancy and showed, at most, only a trace of ankle oedema. In the few early cases hysterotomy was performed for purely medical reasons. These 148 cases have been taken as the control group.

Pre-eclampsia and Eclampsia

The 74 patients with pregnancies complicated by pre-eclampsia and eclampsia included 14 mild pre-eclampsia (delivered at 37–42 weeks) showing an elevation of blood pressure to 140/90 or more and oedema, with slight albuminuria (<1·0 g./litre) in 3 cases, 33 moderate pre-eclampsia (36–41 weeks) with an elevation of blood pressure to 150/100 or more, oedema and albuminuria (up to 6·75 g./litre) in all but 2 cases, 22 severe pre-eclampsia (28–41 weeks) with an elevation of blood pressure (172/100–240/140), oedema and albuminuria (up to 24·0 g./litre) and 5 cases of eclampsia (32–40 weeks), 4 of whom had fits ante-partum.

Essential Hypertension

The 15 patients with essential hypertension (delivered at 33–42 weeks) showed an elevation of blood pressure throughout pregnancy, with a recording of at least 140/90 in early pregnancy. The 4 patients with superimposed pre-eclampsia (32–40 weeks) showed a further elevation of blood pressure, oedema and albuminuria.

Diabetes Mellitus

The 10 patients suffering from diabetes mellitus were delivered at 36–39 weeks. In 9 cases the pregnancy was otherwise normal, only 1 patient showing an elevation of blood pressure (160/100) and some oedema.

Twin Pregnancies

Of the 16 patients with twin pregnancies (delivered at 32–41 weeks), 8 were otherwise normal and 8 showed some degree of pre-eclampsia.

In the majority of cases the duration of pregnancy was accurately known as the patients had attended the antenatal clinic from the early weeks of pregnancy and only those who were certain of the date of the last menstrual period were included in the control group. Some of the patients suffering from pre-eclampsia were non-booked and were examined for the first time on admission to hospital in late pregnancy. Details of early pregnancy were obtainable from the patient's own doctor in a number of these cases. Patients giving a history of vaginal bleeding during pregnancy were excluded from the main groups.

The majority of all the patients had a spontaneous vaginal delivery (trilene analgesia), but some were delivered by forceps or Caesarean section, general, local or spinal anaesthesia being administered.

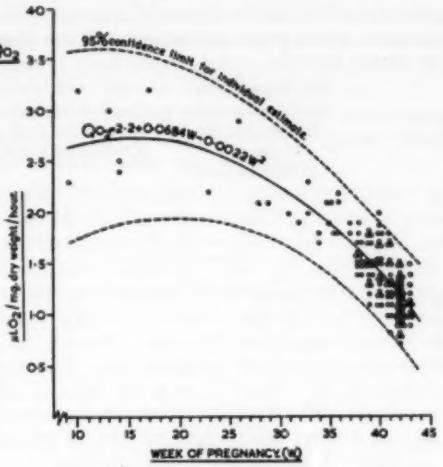


FIG. 1

Individual placental Qo_2 values obtained in 148 clinically normal pregnancies with the estimated regression curve of mean Qo_2 for week of pregnancy and the 95 per cent confidence limits for an individual estimate.

RESULTS

Normal Pregnancy

Figure 1 shows the individual placental Qo_2 readings (μl. oxygen per mg. dry weight of tissue per hour) found in the control group of 148 clinically normal pregnancies. For simplicity of later comparison with the abnormal cases these results have been summarized in an estimated regression equation for the different weeks of pregnancy ($Qo_2 = 2{\cdot}2+0{\cdot}0684W-0{\cdot}0022W^2$) with the 95 per cent confidence limits for an individual estimate* as shown in the figure. Only 1 result falls outwith these limits.

Only 8 specimens were obtained during the first and second trimesters of pregnancy but the Qo_2 values in all of these placentae are well above the results obtained in placentae at term.

In fact the Qo_2 values show a progressive and increasing decline as pregnancy advances beyond the 18th week, this decline being most marked from the 35th to the 43rd week.

The mean Qo_2 value at term is approximately one-half of that found in the early weeks.

Mean Qo_2 values and standard deviations of the normal and the abnormal cases, according to duration of gestation, are shown in Table I.

In the normal pregnancies the mean Qo_2 values show a progressive reduction; 2·0 at 28–35 weeks, 1·7 at 36–38 weeks, 1·4 at 39–41 weeks and 1·1 at 42–43 weeks. In each instance the fall in mean Qo_2 values between successive intervals is statistically significant ($P<{\cdot}001$).

TABLE I

Mean Qo_2 Values and Standard Deviations of the Normal and Abnormal Cases after Subdivision for Maturity

Duration of Pregnancy (Weeks)	Pregnancy	No. of Cases	Mean Qo_2	Standard Deviation
28–35	Normal	11	2·0	±0·17
	Pre-eclampsia and eclampsia ..	9	0·9	±0·28
(36–37)	Normal	6	1·9	±0·18
	Diabetes mellitus	9	1·6	±0·23
36–38	Normal	19	1·7	±0·22
	Pre-eclampsia and eclampsia ..	26	1·2	±0·26
39–41	Normal	60	1·4	±0·26
	Pre-eclampsia and eclampsia ..	37	1·1	±0·23
	Essential hypertension	8	1·3	±0·21
	Twins (normal)	8	1·1	±0·23
	Twins (pre-eclampsia)	8	0·9	±0·23
42–43	Normal	50	1·1	±0·20

* See Statistical Note on page 799.

TABLE II

Number of Results from Pre-eclamptic and Eclamptic Pregnancies Falling Within and Below the 95 Per Cent Confidence Limit for the Normal Controls

Severity	Total No. of Cases	Qo_2 Values Below the Control Mean But Within the 95 per cent Confidence Limit	Qo_2 Values Below the 95 per cent Confidence Limit
Mild pre-eclampsia	14	14	—
Moderate pre-eclampsia	33	24	9
Severe pre-eclampsia	21	7	14
Total Duration			
Up to 3 weeks	38	27	11
Over 3 weeks	35	21	14
Over 4 weeks	20	9	11
Over 5 weeks	13	5	8

To summarize, there is a fall in the rate of oxygen consumption of fresh placental tissue as normal pregnancy advances to term and continues beyond the expected date of delivery, the reduction in the rate of consumption being most marked in the later weeks.

Pre-eclampsia and Eclampsia

The individual placental Qo_2 readings obtained in the 74 patients suffering from pre-eclampsia and eclampsia are shown in Figure 2 against the regression curve and the 95 per cent confidence limits for the normal controls.

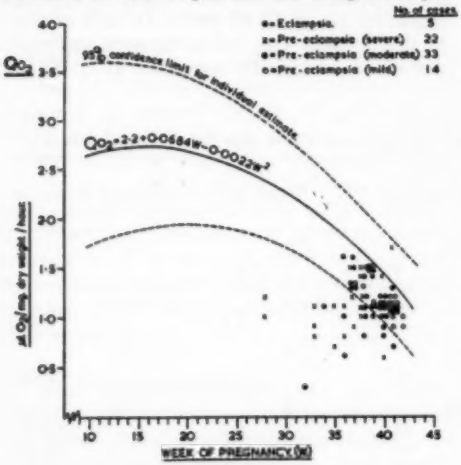


FIG. 2

Individual placental Qo_2 values obtained in 74 cases of pre-eclampsia and eclampsia with the estimated mean Qo_2 and 95 per cent confidence limits for the control group of 148 normal pregnancies (as shown in Fig. 1).

The Qo_2 values obtained in these 74 cases are clearly below the mean of the normal controls. In only 1 case, delivered at 41 weeks (Qo_2 1·7), is the Qo_2 value higher than the mean of the controls. In this severe case the pre-eclampsia was of known short duration. The patient had been attending the antenatal clinic regularly and had been free from all signs and symptoms of pre-eclampsia until the 39th week of pregnancy, when she showed some ankle oedema and a slight elevation of blood pressure (135/85). The pre-eclampsia was of the fulminating type, albuminuria, marked hypertension (180/110), headaches and visual disturbances occurring for the first time during labour.

The remaining 73 cases have been divided into 2 groups according to the magnitude of the deviation of their Qo_2 values from the mean of the normal pregnancies. It was found convenient to take as the dividing line the 95 per cent confidence limit for the normal controls.

Table II gives the number of cases falling into these two groups with reference to (*a*) the severity of the pre-eclampsia irrespective of the total duration of the complication and (*b*) the total duration of the pre-eclampsia irrespective of its severity. Owing to the fact that estimation of the total duration of the complication had to be made from available records or, in the non-booked cases, from the patient's history, this estimation cannot be absolutely accurate in

every instance. However, Table II illustrates the tendency for the more severe cases and for the cases of total longer duration to fall below the confidence limit for the normal controls.

In the following section some of the clinical details of the 73 cases giving Qo_2 values below the control mean are presented:

Mild Pre-eclampsia (14 cases). As shown in Table II, the Qo_2 values of all 14 cases of mild pre-eclampsia (37–42 weeks) fall within the confidence limit for the normal controls. Labour was induced by artificial rupture of the membranes in 8 of these patients, in 7 instances after the 40th week of pregnancy. In only 3 cases was there evidence that the pre-eclampsia had existed for over 4 weeks. All 14 infants survived.

Moderate Pre-eclampsia (33 cases). (*a*) The Qo_2 values of 24 (73 per cent) of the 33 cases of moderate pre-eclampsia fall within the confidence limit for the controls. Of these 24 patients (delivered at 37–41 weeks), only 6 had shown evidence of pre-eclampsia for more than 4 weeks. Labour was induced in 12 cases and a further 2 patients were delivered by elective Caesarean section, the indications being other than the severity of the pre-eclampsia.

(*b*) In 6 of the 9 patients (36–41 weeks) giving Qo_2 values below the confidence limit, some signs of pre-eclampsia had existed for over 4 weeks. Pregnancy was terminated in 5 of the 9 patients. In 4 cases, 2 at 36 weeks (Qo_2 0·6, 1·0) and 2 at 38 weeks (Qo_2 0·8, 1·0), this was carried out because of the increasing severity of the pre-eclampsia, particularly the increasing albuminuria. All 33 infants survived.

Severe Pre-eclampsia (21 cases). (*a*) The Qo_2 values of only 7 (33 per cent) of the 21 cases of severe pre-eclampsia fall within the confidence limit. Six of these 7 (37–41 weeks) were booked cases and, in all 6, the total duration of the pre-eclampsia was less than 4 weeks. The non-booked patient was reputed to have shown some signs and symptoms of pre-eclampsia for 2–3 weeks prior to admission. Although the complication was not severe on admission (B.P. 150/90), the patient's condition rapidly deteriorated (B.P. 200/130, albuminuria 20 g./litre) and she was delivered by Caesarean section 4 days later. Pregnancy was terminated by induction of labour or Caesarean section in all 7 cases because of the increasing severity of the pre-eclampsia. All 7 infants survived.

(*b*) Of the 14 cases of severe pre-eclampsia giving Qo_2 values below the confidence limit for the controls, 6 had shown some evidence of pre-eclampsia, such as a slight elevation of blood pressure, or an excessive weight gain, or oedema for 4 weeks or more. In these 6 patients the Qo_2 values are very low: 1·0 (28 weeks), 0·9 (33 weeks), 0·7 (35 weeks), 1·1 (36 weeks), 0·9 (37 weeks) and 0·6 (40 weeks). In 11 of the 14 patients pregnancy was terminated on account of the increasing severity of the pre-eclampsia (7 induction of labour, 4 Caesarean section). The remaining 3 patients went into labour spontaneously at 35, 37 and 38 weeks. Four of the 14 infants died during labour or shortly afterwards.

Eclampsia (5 cases). (*a*) The Qo_2 values of 3 cases of eclampsia fall within the confidence limit. All were booked cases. The patient delivered at 36 weeks (Qo_2 1·6), was examined at 32 weeks (B.P. 118/74) and returned to the antenatal clinic 4 weeks later, giving a history of swelling of her hands and ankles for 10–14 days. She was immediately admitted to hospital with gross oedema, albuminuria (14 g./litre) and a blood pressure of 175/110. She went into labour on the following day and had 2 fits immediately after delivery. The patient delivered at 37 weeks (Qo_2 1·3) showed no signs or symptoms of pre-eclampsia 14 days before delivery. The third patient (Qo_2 1·1 at 40 weeks) had defaulted from the clinic for about 6 weeks. On return to the clinic she was found to be suffering from severe pre-eclampsia but gave a short history of symptoms. She was admitted at once and labour was induced on the following day. These latter 2 patients each had 1 ante-partum fit. All 3 infants survived.

(*b*) The 2 cases of eclampsia giving Qo_2 values below the confidence limit were also booked. One at 32 weeks (Qo_2 0·3) had 3 fits prior to admission. Labour was induced after sedation with avertin and the patient delivered spontaneously. Although the foetal heart was heard just before delivery, the infant was still-born. This patient had shown a slight elevation

of blood pressure from 115/70 to 130/80 and an excessive weight gain 4 weeks before admission. The second patient (Qo_2 1·1 at 34 weeks) had 3 ante-partum fits following admission. Labour was induced. The infant died on the 3rd day. This patient showed some excessive weight gain and a slight elevation of blood pressure to 135/80, 2 weeks before delivery.

As previously noted, all 74 cases of pre-eclampsia and eclampsia, irrespective of the severity of the complication, have been grouped according to the duration of gestation, mean Qo_2 values being shown in Table I. As will be seen from Figure 2, the more severe cases tend to fall into the earlier groups, pregnancy being terminated at an earlier date.

In the 9 cases of pre-eclampsia and eclampsia delivered at 28–35 weeks the mean Qo_2 is 0·9, compared with 2·0 in the 11 controls (see Table I). At 36–38 weeks the mean value (26 cases) is 1·2 compared with the control mean of 1·7 (19 cases). At term the mean value (37 cases) is 1·1 compared with the control mean of 1·4 (60 cases). The difference in mean values is most marked in the earlier periods, but all the differences are statistically significant ($P < \cdot001$).

To summarize, there is a reduction in the rate of oxygen consumption of apparently healthy fresh placental tissue from pre-eclamptic and eclamptic pregnancies compared with that found in normal pregnancies of the same duration. The degree of this reduction appears to be related to the total duration of the pre-eclampsia as well as to its severity.

Essential Hypertension

The 15 patients suffering from essential hypertension were delivered at 33–42 weeks, 5 by elective Caesarean section. All were booked cases and in early pregnancy the blood pressure was 140/90 to 178/100. The majority showed a further elevation of blood pressure in late pregnancy or during labour (156/90–190/120), but no albuminuria, and no more than a trace of ankle oedema. The individual Qo_2 values obtained are shown in Figure 3 against the regression curve and confidence limits for the normal controls.

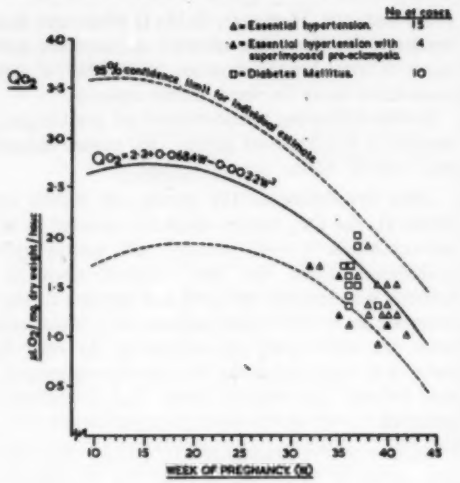

No. of cases
Δ = Essential hypertension 15
▲ = Essential hypertension with superimposed pre-eclampsia 4
□ = Diabetes Mellitus 10
95% confidence limit for individual estimate
$Qo_2 = 2·3 + 0·0684W - 0·00329W^2$
μl O2 / mg dry weight / hour
WEEK OF PREGNANCY (W)

FIG. 3

Individual placental Qo_2 values obtained in cases complicated by essential hypertension and diabetes mellitus with the estimated mean Qo_2 and 95 per cent limits for the normal pregnancies.

All but 2 of the placental Qo_2 values fall well within the 95 per cent confidence limits of the controls. The 2 results below the confidence limit are 1·1 at 36 weeks and 0·9 at 39 weeks. These 2 patients were over 40 years of age and showed the highest blood pressure recordings in early pregnancy (176/90 at 10 weeks, 178/100 at 14 weeks). Both were controlled by Serpasil during pregnancy and both were delivered by elective Caesarean section. In both instances the placentae were relatively small compared with the size of the foetus (12½ ounces, 5 pounds 1¾ ounces; 15½ ounces, 7 pounds 2 ounces).

When the mean Qo_2 value of the 8 hypertensive cases at 39–41 weeks (Qo_2 1·3—see Table I) is compared with that of the 60 normal pregnancies at term (Qo_2 1·4), the difference is not shown to be significant ($P > \cdot2$).

With the possible exception of the 2 more severe cases in which the complication had probably existed for some time, the presence of essential hypertension does not appear to be related to any change in the placental Qo_2 values.

The Qo_2 values in the 4 patients with essential hypertension who subsequently developed some degree of superimposed pre-eclampsia, with albuminuria, are all below the control mean, 1 being below the confidence limit (see Fig. 3).

Diabetes Mellitus

All 10 patients suffering from diabetes mellitus were delivered by elective Caesarean section (36–39 weeks).

Almost all the individual placental Qo_2 values, shown in Figure 3, fall within the confidence limits for the normal controls, 1 result (Qo_2 1·3 at 36 weeks) being just below the confidence limit. The Qo_2 value of the patient who developed hypertension (160/100) and oedema in late pregnancy was 1·7 at 36 weeks, a value just below the control mean.

The mean Qo_2 value (1·6) of the 9 cases delivered at 36–37 weeks compares with a value of 1·9 in the 6 normal pregnancies at the same period of gestation (see Table I). Although there is some evidence that the difference in mean values may be significant ($P < \cdot 05$), the number of cases is too small for firm conclusions to be drawn. Further cases of diabetes mellitus are, therefore, being studied and will be reported on at a later date.

Twin Pregnancies

Patients with multiple pregnancies were excluded from the previous groups but the placentae of 16 patients with twin pregnancies were investigated and the results obtained are of some interest.

Estimation of Qo_2 values was carried out simultaneously on the two placentae, or on the two parts of the single placenta. In some instances there was a slight difference in the two results obtained, usually 0·1–0·2 Qo_2.

Of 8 patients with otherwise normal pregnancies, 4 (33–40 weeks) had uniovular twins, mean Qo_2 of the 8 specimens being 1·3. The mean value obtained in the remaining 4 patients, delivered of binovular twins (32–41 weeks), was also 1·3. In the 4 patients delivered at 39–41 weeks (2 uniovular, 2 binovular) the mean Qo_2 was 1·1, compared with 1·4 in normal singleton pregnancies at term (see Table I). This difference in mean values is significant ($P < \cdot 01$).

Four of the 8 patients suffering from pre-eclampsia had uniovular twins (34–37 weeks). The mean Qo_2 was 1·3. The remaining results from binovular twins are not comparable with this mean as all 4 patients were delivered at 39–40 weeks (mean Qo_2 0·9). The latter figure is, however, comparable with the values obtained in normal (1·4) and pre-eclamptic (1·1) singleton pregnancies at term (see Table I). In both instances the difference in levels is significant ($P < \cdot 001$, $P < \cdot 05$).

The average rate of oxygen consumption of placental tissue from twin pregnancies is lower than that found in singleton pregnancies. In the presence of pre-eclampsia, the rate of oxygen consumption is further reduced.

Discussion

The reduction in the rate of oxygen consumption of fresh placental tissue during the course of normal pregnancy shows a trend similar to that observed by earlier authors, such as Loeser (1932), Wang and Hellman (1943), Page (1948), Hellman, Harris and Andrews (1950) and Villee (1953). The actual figures and the precise pattern of the findings obtained in these studies do, however, differ in some respects, e.g., Wang and Hellman (1943) found a mean Qo_2 of 1·7 in 18 cases at term, while Hellman, Harris and Andrews (1950), recorded values with a mean Qo_2 of 2·6 in 34 cases at 39–41 weeks. These variations are very probably due to slight modifications in the Warburg technique such as the method of estimating dry weights, the atmosphere used, the addition of glucose to the substrate, etc.? Villee (1953) observed relatively little change in the rate of oxygen consumption from the 30th week to term, whereas Page (1948) recorded a significant reduction during the last trimester of pregnancy.

Particular reference has not been made by these authors to the effects of postmaturity but several observations include results from pregnancies which have continued beyond the expected date of delivery, e.g., Page (1948) demonstrating the continued reduction in Qo_2 values after the 40th week of pregnancy.

This reduction in the placental Qo_2 values as normal pregnancy advances to term and con-

tinues thereafter is consistent with the histological changes, associated with degeneration, shown in the villi. It is not surprising that these changes should to some extent interfere with the aerobic metabolism of the individual cells. It is to be thought that these degenerative processes continue after the 40th week, by which time the uterine blood flow has been shown to be further reduced (Moore and Myerscough, 1957).

None of the placentae from normal pregnancies showed extensive macroscopic degeneration although some, particularly those from the later weeks studied, showed a fairly marked degree of calcification. There was a progressive increase in the dry weight : wet weight ratio of the placental tissue as pregnancy advanced (also observed by Villee, 1953) but this alone did not account for more than a fraction of the reduction in Qo_2 values.

The senescent changes occurring in the course of normal pregnancy have been shown by many authors to be accelerated in the presence of pre-eclampsia, e.g., Tenney and Parker (1940), Wislocki and Dempsey (1946). This can be correlated with the reduction observed in both the chorio-decidual (Browne and Veall, 1953) and the myometrial blood flow (Morris, Osborn and Payling-Wright, 1955; Johnson and Clayton, 1957; Moore and Myerscough, 1957) in patients suffering from pre-eclampsia.

The reduction in the rate of oxygen consumption demonstrated in the placental tissue from pregnancies complicated by pre-eclampsia and eclampsia follows the expected pattern, the lowest values being obtained in the more severe cases and in those in which the complication had existed for some weeks. These findings are to some extent in agreement with both those of Page (1948) and those of Hellman, Harris and Andrews (1950) and Villee (1953). Page (1948), as well as demonstrating some very low Qo_2 values in cases of severe pre-eclampsia and eclampsia in which the complication had existed for some weeks, observed that some values obtained in moderate cases, particularly if of short duration, were well within normal limits. Villee (1953) and Hellman and his fellow workers (1950) were concerned with the effects of severe, acute pre-eclampsia, the latter specifying that no patient showed hypertension for more than 3 weeks. Although no significant change from normal levels was shown in either of these investigations, this may well have been due to the acute nature of the pre-eclampsia, little degeneration having occurred in the relatively short space of time.

In this study the experiments were carried out only on areas of apparently healthy tissue, areas of infarction being avoided. The results quoted do not, therefore, give any absolute indication of the possible oxygen requirements of the placenta as a whole, but merely an indication of the relative requirements of the healthier parts of the organ. In a number of the placentae from pre-eclamptic and eclamptic pregnancies an appreciable degree of gross degeneration was present. Such areas, when separately investigated, gave minimal Qo_2 values but as it was impossible to estimate accurately the precise fraction of the placenta affected, no attempt was made to obtain a figure which expressed the rate of oxygen consumption of the organ as a whole. It is not, therefore, suggested that the above findings give a true indication of placental ageing or functional capacity. They merely demonstrate, that in so far as the rate of oxygen consumption reflects the senescence of the healthier areas of the organ, there is probably an acceleration in ageing and therefore some functional limitation in the presence of pre-eclampsia and eclampsia, particularly if severe or of some weeks duration. The presence of gross degeneration in the form of infarcts would, of course, cause further functional limitation. The figures obtained in this study would, therefore, considerably underestimate failure of function.

With regard to the presence of essential hypertension, without superimposed pre-eclampsia, as a complication of pregnancy, significant change in the rate of oxygen consumption was not demonstrated. This confirms the findings of Wang and Hellman (1943) and Hellman, Harris and Andrews (1950) and is consistent with the absence of specific histological changes in the placentae of such cases (Tenney and Parker, 1940). The 2 patients giving low Qo_2 values were elderly and most probably some arteriosclerotic changes limited placental nutrition.

The results obtained in pregnancies complicated by diabetes mellitus are at present inconclusive. Relatively few cases (10) have been studied and it will be advantageous to continue this aspect of the investigation to establish whether or not the placental Qo_2 values are, in fact, lower than normal.

The lower rates of oxygen consumption demonstrated in placental tissue from twin pregnancies, particularly those with some degree of pre-eclampsia, are consistent with a possible inadequacy of placental nourishment.

Summary

(1) Observations of the rate of oxygen consumption of fresh placental tissue were made on specimens from 267 pregnancies.

(2) In 148 normal pregnancies the rate of oxygen consumption is shown to be significantly reduced as pregnancy advances to term and continues beyond the expected date of delivery. The mean Qo_2 value in 60 cases at 39–41 weeks is $1{\cdot}4 \pm 0{\cdot}26$.

(3) In 74 pregnancies complicated by pre-eclampsia and eclampsia the average rate of oxygen consumption is significantly lower than that found in normal pregnancies of the same duration. The mean Qo_2 value in 37 cases at 39–41 weeks is $1{\cdot}1 \pm 0{\cdot}23$. The degree of the reduction appears to be governed by the total duration as well as by the severity of the complication.

(4) In 15 pregnancies complicated by essential hypertension there is no significant change from normal levels.

(5) In 10 pregnancies complicated by diabetes mellitus the results are inconclusive. Further cases are under investigation.

(6) In 16 twin pregnancies there is a reduction in the rate of oxygen consumption, particularly in the presence of pre-eclampsia.

Statistical Note

The regression curve, $Qo_2 = 2{\cdot}2 + 0{\cdot}0684W - 0{\cdot}0022W^2$ (W = week of pregnancy), represents the best estimate of the average Qo_2 values for each week of pregnancy. This estimate is inevitably affected by (1) variation in the original data and (2) the assumed normal variation in Qo_2 which occurs at any particular week.

These two sources of variation may be conveniently combined to provide limits within which an individual Qo_2 reading for a specified week of pregnancy may be estimated to lie.

The assumption is that the estimated individual Qo_2 values for any specified week will lie in a symmetrical distribution about an average value, i.e., the value given by the regression curve. On this assumption, and on the assumption that the basic data are not biassed in any relevant way, we may interpret the outside limit lines as meaning that for any week of pregnancy we would expect 95 out of 100 estimates of an individual value to lie within these limits. For convenience these limits are therefore called the "95 per cent confidence limits".

Acknowledgments

This investigation was undertaken at the request of Professor R. J. Kellar and I have to thank him and his colleagues on the staff of the Simpson Memorial Maternity Pavilion for the provision of clinical material. I am indebted to Mr. S. A. Sklaroff, B.Sc., of the Department of Public Health and Social Medicine, University of Edinburgh, for statistical advice. I must also acknowledge the assistance given by my technician Mrs. S. W. Nisbet, A.I.M.L.T., and the co-operation of Sister Anderson and her staff in the Labour Ward.

References

Browne, J. C. M., and Veall, N. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 141.

Hellman, L. M., Harris, B. A., Jr., and Andrews, M. C. (1950): *Bull. Johns Hopk. Hosp.*, **87**, 203.

Johnson, T., and Clayton, C. G. (1957): *Brit. med. J.*, **1**, 312.

Loeser, A. (1932): *Arch. Gynäk.*, **148**, 118.

Moore, P. T., and Myerscough, P. R. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 207.

Morris, N., Osborn, S. B., and Payling-Wright, H. (1955): *Lancet*, **1**, 323.

Page, E. W. (1948): *Obstet. Gynec. Surv.*, **3**, 615.

Rech, W. (1924): *Z. Biol.*, **80**, 231.

Tenney, B., Jr., and Parker, F., Jr. (1940): *Amer. J. Obstet. Gynec.*, **39**, 1000.

Villee, C. A. (1953): *J. biol. Chem.*, **205**, 113.

Wang, H. W., and Hellman, L. M. (1943): *Bull. Johns Hopk. Hosp.*, **73**, 31.

Wislocki, G. B., and Dempsey, E. W. (1946): *Endocrinology*, **38**, 40.

THE TREATMENT OF BARTHOLIN'S CYSTS BY MARSUPIALIZATION

BY

D. H. BLAKEY, M.B., M.R.C.O.G.

Lecturer in Obstetrics and Gynaecology
University of Sheffield

THE uncomplicated Bartholin's cyst is a minor disorder which causes very few symptoms, so its treatment should be simple and should leave the patient symptom-free. But this is not so; conventional treatment by excision of the cyst can be very troublesome, recurrence may follow unless the gland too is excised and considerable discomfort may be suffered because of painful scarring or loss of secretion.

Several accounts have been published in the United States in recent years (Davies, 1948; Jacobson, 1950; Wilder, 1955; Tancer, Rosenberg and Fernandez, 1956) describing a method of treatment which is notable for its simplicity and freedom from complication, and unique in its offer of restoration of function. The procedure has been tried in Sheffield with such encouraging results that this report is offered in the belief that the operation deserves to be more widely known.

TECHNIQUE

Bartholin's cyst is a dilatation of the 2 cm. long duct due to blockage at its distal end where it opens into the vagina. The operation is an attempt to reconstruct the damaged muco-cutaneous junction without interfering at all with the deeper portions of cyst wall or gland. A vertical incision ¾–1 inch long is made directly into the cyst on its vaginal aspect, just outside the hymenal ring, ending inferiorly about the site of the normal opening of the duct. After emptying its contents, the lining of the cyst is sutured to each adjacent cut skin margin so that when healed a permanent opening will remain. About 6 catgut sutures are usually required (Fig. 1).

No drainage is necessary and after-care consists in simple hygiene with daily baths only. The operation is extremely simple, taking only a few minutes, and involves negligible blood loss. In the absence of infection it can be performed under local analgesia and has been satisfactorily done on out-patients. Healing is usually rapid and haematomata do not occur; in-patients are able to return home in 3 or 4 days. It is a particularly suitable form of treatment during pregnancy when increased vascularity makes excision more difficult.

RESULTS

The operation has been done 14 times in the last 2½ years (Table I). Three were performed on out-patients. Local analgesia was used 5 times. The lesion was a chronic cyst in 8 cases, but a variable degree of infection was found at the time of operation in 6 others and the lesion was described as an abscess. The presence of a thick capsule in each of the abscesses suggested that infection had arisen in a pre-existing cyst. A swab was taken for culture in the infected cases; 3 remained sterile and in 3 others *Escherichia coli* was isolated.

Four of the cases were operated upon during the early months of pregnancy. The first, in whom the incision had been rather too short, developed a recurrent swelling a few weeks after operation and was re-admitted for treatment.

FIG. 2

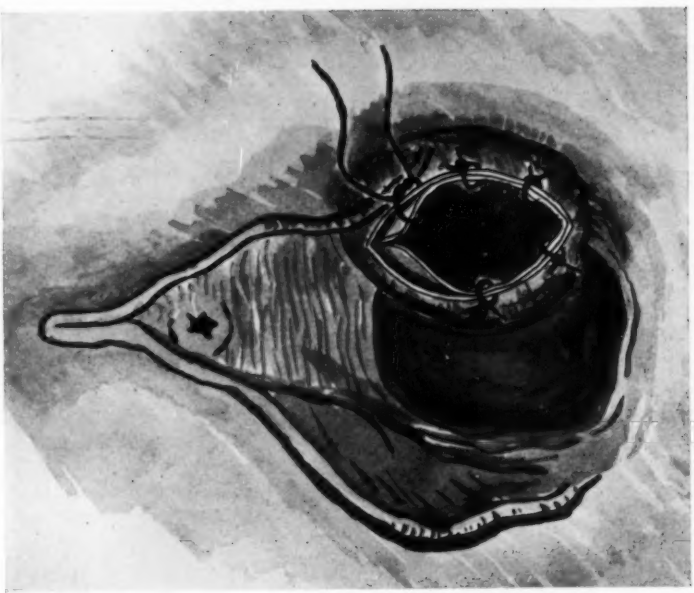


FIG. 1

TABLE I

Details of Cases Treated by Marsupialization

Case No.	Lesion	G.A. or Local	Days in Hospital	Culture	Time Since Operation	Remarks
1 ..	Cyst	Local	4	Nil	8 months	Operation at 20 weeks pregnancy.
2 ..	Cyst	G.A.	7	Nil	19 months	Operation at 36 weeks pregnancy.
3 ..	Cyst	Local	5	Nil	2½ years	Operation at 22 weeks pregnancy.
4 ..	Cyst	G.A.	4	Nil	1 year	
5 ..	Cyst	G.A.	6	Nil	9 months	8 years history.
6 ..	Cyst	Local	O.P.	Nil	3 months	Previous excision of cyst on opposite side.
7 ..	Cyst	Local	O.P.	Nil	15 months	Bilateral cysts on same patient.
8 ..	Cyst	Local	O.P.	Nil	3 months	
9 ..	Abscess	G.A.	6	Sterile	3 months	
10 ..	Abscess	G.A.	7	Sterile	18 months	
11 ..	Abscess	G.A.	4	Sterile	2 months	
12 ..	Abscess	G.A.	4	*E. coli*	21 months	Operation at 25 weeks pregnancy. 9 previous visits in 6 years.
13 ..	Abscess	G.A.	7	*E. coli*	18 months	Previous abscess on opposite side.
14 ..	Abscess	G.A.	4	*E. coli*	2 months	

The end result was satisfactory in all 14 cases.

The duration of stay in hospital shown above was determined by convenience rather than necessity. Most of them were quite fit to return home after 3 days.

Infection subsided with rest and local bathing and did not recur. When she was last seen 2 years later a sinus persisted and there had been no further trouble.

Thirteen patients have been re-examined between 3 months and 2 years after operation; all were well pleased with the result and none complained of any residual symptoms. Though in each case the hole had shrunk to a considerable degree, a sinus persisted about ¼ inch in diameter. The appearances were the same regardless of the nature of the original lesion; the end result of cyst and abscess treated in the same way seemed to be identical (Fig. 2).

DISCUSSION

The treatment of Bartholin's cysts by excision involves a moderately difficult dissection in a highly vascular area. Accurate haemostasis is not easy and post-operative haematomata are common. Healing, especially when complicated by infection, may lead to considerable distortion, and residual scarring may so reduce the elasticity of the tissues that should a swelling recur it will be more painful than the original lesion. Loss of secretion should not cause symptoms as long as one gland is healthy, but bilateral disease is common, and excision of both can be responsible for a good deal of discomfort. Though this has not often been described, Jacobson (1950) reports a convincing case.

All these difficulties can be avoided by the technique described, which in addition is so much simpler and quicker to perform, and is far and away more comfortable for the patient. Another advantage of this method is that it can easily be done at once, as an out-patient if desired, whilst the cyst is full; so avoiding the common experience of admitting such a case from a waiting list only to find that the cyst contents have escaped spontaneously and there is nothing to see. Two short case histories illustrate this contrast: one patient made 9 separate visits to the gynaecological departments of the Sheffield hospitals over a period of 6 years on account of a Bartholin's cyst. Three times she was admitted, but was twice discharged again because there was nothing to see. Twice an abscess was incised, but always the lump returned, until finally, at the 25th week of a

pregnancy, she was admitted yet again, and a thick-walled abscess was incised and marsupialized. It is now nearly 2 years since this operation; she has had no further symptoms and is delighted with the result (Fig. 2). Another patient had a cyst marsupialized over a year ago, and returned to the out-patient department with another cyst on the opposite side. At this first visit with the second cyst the operation was done "whilst she waited", and she has had no further trouble with either. This case is a testimony to the success of the procedure from the patient's point of view: she did not confess when immediate operative treatment was suggested for the second cyst that she had arranged to go to a social function 4 days later. When seen in the follow-up clinic one week afterwards and asked what inconvenience the treatment had caused, she announced that she had been to a most successful dinner dance nearly 40 miles away. Though in-patient treatment under general anaesthesia is usually preferred, if there are factors which make it desirable the operation can be done on out-patients at very short notice.

Both cysts and abscesses can be treated similarly provided the lining is not too friable to be sutured. Wilder (1955) reports 32 cysts and 48 abscesses treated by marsupialization with equally good results. If incision only is performed, the lining collapses and granulates over so that blockage of the duct persists and recurrence is likely. Davies (1948) did not suture the cyst lining to skin, but attempted to preserve a permanent sinus by packing the cavity with iodoform gauze twice weekly for 3 or 4 weeks. This was not entirely successful as intermittent dilatation was later required in some cases to relieve stenosis. Jacobson (1950), whose paper was the first to describe marsupialization and includes a full, well-reasoned account of the whole subject, exposed a moderate area of cyst wall by dissection of the skin flaps before opening the cyst. Experience of the cases reported here suggests that this is not necessary, but that an adequate opening will be preserved if a direct incision is made through skin and cyst wall for $\frac{3}{4}$ inch or more, and these two layers are sutured together; there is no need to insert painful gauze dressings for drainage.

Though the bacteriological findings support the view that the great majority of Bartholin's cysts and abscesses in this country are not venereal in origin, the recent isolation of gonococci from an acute abscess serves as a reminder that culture should not be omitted.

Three patients have had cysts on both sides; one of them has had experience both of excision and of marsupialization. When asked which was the better she was emphatic in her choice of the latter operation.

Conclusions and Summary

Marsupialization of Bartholin's cyst is a better treatment than excision. It is much simpler to perform and has fewer complications. It can be done under local analgesia in an out-patient department, so that intermittent swellings can easily be dealt with whilst there is something to see. Chronic abscesses can be treated by the same operation with equally good results. This is the only form of therapy which preserves the function of the gland.

Personal observation of the simplicity of marsupialization and its uniformly excellent results forces me to the conclusion that there is no longer any place for excision of Bartholin's cyst, and in my opinion this orthodox procedure should be abandoned.

Fourteen cases are described, 8 cysts and 6 abscesses, which have been treated by marsupialization with complete success.

Acknowledgments

I wish to thank Professor C. S. Russell who first drew attention to the description of this operation, recognized its possibilities and encouraged its use.

My thanks are also due to Mr. Joseph Larway, Department of Medical Photography, United Sheffield Hospitals, for the illustration.

References

Davies, J. W. (1948): *Surg. Gynec. Obstet.*, **86**, 329.

Jacobson, P. (1950): *West. J. Surg. Obstet. Gynec.*, **58**, 704.

Tancer, M. L., Rosenberg, M., and Fernandez, D. (1956): *Obstet. Gynec.*, **7**, 608.

Wilder, E. M. (1955): *Sth. med. J.*, **48**, 460.

A STUDY OF THE VESSELS OF THE PLACENTAL BED IN NORMOTENSIVE AND HYPERTENSIVE WOMEN

BY

H. G. DIXON, M.B., M.R.C.P.(Ed.), M.R.C.O.G.
Senior Lecturer in Obstetrics and Gynaecology

AND

W. B. ROBERTSON, B.Sc., M.B.
Senior Lecturer in Morbid Anatomy
University College of the West Indies, Jamaica, B.W.I.

SINCE the observation by Young (1914) of the increased frequency of red infarcts in the placentae of eclamptic women the concept that pre-eclampsia owed its origin to some malfunction of the placenta has continued to gather support. Much detailed histological work has been carried out on the separated placenta but this has been, to say the least, inconclusive (Bartholomew *et al.*, 1957; Colvin and Bartholomew, 1938; Tenney, 1936). The study of Russell *et al.* (1957) shows that the vascular and stromal changes and the syncytial atrophy normal in the aging placenta are accelerated in the presence of pre-eclampsia and essential hypertension. As the foetal chorion is completely dependent upon the maternal blood supply it seems that the changes in the delivered placenta must be secondary to alterations on the maternal side of the placenta, and here one should find the initial lesions.

The first direct evidence of the reduced maternal blood flow through the placenta in pre-eclampsia and essential hypertension was provided by Browne and Veall (1953). Subsequently Morris, Osborn and Wright (1955), using a technique basically similar to that of Browne and Veall except that the Na^{24} was injected into myometrium rather than into the chorio-decidual space, demonstrated a similar reduction in blood flow through the myometrium. This observation has been confirmed by Johnson and Clayton (1957). The initial work of Browne and of Morris has been extended (1957) and not only have the first results been confirmed but there appears to be a correlation between the reduction in myometrial and placental blood flow rates in the presence of maternal hypertension.

Much work has been done by Assali *et al.* (1953) and Metcalfe *et al.* (1955) to measure the uterine blood flow using the nitrous oxide technique. In the normal pregnant woman the values obtained have been in fairly close agreement with the figure calculated by Browne and Veall. The results of this school of investigators in the field of hypertensive pregnancy are still awaited.

The problem as to whether the reduction in utero-placental blood flow is the cause of the hypertension or its effect is as yet unsolved.

Working on animals Ogden, Hildebrand and Page (1940) and Bastiaanse and Mastboom (1949) produced hypertension by partial occlusion of the uterine blood supply during pregnancy. A similar rise of blood pressure could not be produced in the non-pregnant animal. Page (1948) gave vigorous support to the suggestion that placental hypoxia is the initiating factor in the pre-eclamptic process, and certain biochemical evidence, notably that of Thompson and Tickner (1949), has been produced to strengthen this hypothesis.

In contrast Browne and Veall state their belief that the reduction in blood flow is

secondary to the hypertension, basing this statement on their observation that the reduction in flow was similar in amount whether the woman was suffering from pre-eclampsia or essential hypertension.

It appeared that some light might be thrown on this problem by a detailed examination of the blood vessels on the maternal side of the placenta and comparing any changes found with those known to occur elsewhere in the body in essential hypertension.

Changes in the decidual vessels have been described by Hertig (1945), Sexton *et al.* (1950) and by Zeek and Assali (1950), the essential lesion being a degenerative arteriolitis or "acute atherosis". These authors, however, were aware of the inadequacy of their material and urged that further study of the maternal vessels should be undertaken. Post-mortem specimens are, happily, of rare occurrence and even when obtained are often unsuitable because of autolysis which may be enhanced by infection. Post-partum hysterectomy specimens are of doubtful value as the rapid involution of the puerperal uterus produces extensive changes in the vessels. In the normal process of placental separation the vast majority of maternal vessels remain *in situ*. Zeek and Assali used an ingenious technique for the study of decidual vessels from the placenta and membranes as delivered but were unable to obtain more than short segments of vessels for examination. They were, of course, unable to obtain any picture of the vessel changes in the myometrium except in hysterectomy and autopsy specimens. Owing to these manifold difficulties the exact nature of the vessel changes in the placental bed, their time of onset and the diversity of conditions under which they can occur, are unknown.

What is believed to be a new technique for obtaining material suitable for the histological examination of the vessels in the placental bed has been used in the present investigation and this paper records the findings in the first 36 cases to be investigated.

Material and Methods

At Caesarean section, unless the discretion of the operator dictated otherwise, a biopsy has been taken from the placental bed. This was obtained by means of a cervical punch biopsy forceps. In the earlier cases the placental site was located and marked digitally before delivery of the placenta was complete, but latterly the biopsy forceps has been thrust through the placenta before separation was complete peripherally. It is usually possible to obtain two or three biopsies from each case. These are placed at once into 10 per cent neutral buffered formal-saline. The placenta and membranes are similarly treated so that if required the whole thickness of placenta from amnion to myometrium is available for histology.

The series has been extended by the inclusion of the few Caesarean hysterectomy and hysterotomy specimens available.

The biopsies and blocks of the placental bed from the hysterotomy and hysterectomy cases were processed in the usual manner, care being taken to align the tissue so that both myometrium and decidua were included in the sections. A minimum of eight serial sections was cut from each block, and in some cases considerably more. Haemalum and eosin was employed as a routine stain but in each case sections were also stained by a modified Mallory's Trichrome technique and the Periodic Acid Schiff method. In this manner vessels showing pathological changes could be followed and the type of change more fully assessed by the special stains.

The patients studied were of mixed races but predominantly African and they were classified clinically into two main groups: (*a*) hypertensive and (*b*) normotensive. An attempt was made to subdivide them further, but difficulty was encountered with the hypertensive group. Owing to the relatively late antenatal bookings in Jamaica and the paucity of records available for those patients who had had previous confinements at home it was not always possible to differentiate the "pure" pre-eclamptics from those in whom pre-eclampsia had been superadded to an existing hypertension. The subsequent histological findings suggested, however, that this differentiation was of little importance and 2 cases were included as essential hypertension with super-added pre-eclampsia on the basis of retrospective clinical assessment only.

TABLE I

Classification		Total	Normal Vessels	Hypertensive Changes	Other Changes
Normotension		15	14	0	1*
Essential hypertension	Mild	5	3†	2	0
	Severe	1	0	1	0
Pre-eclampsia		2	0	2	0
Essential hypertension with pre-eclampsia		5	0	5	0
Eclampsia		2	0	2	0
Renal impairment	Normotensive	1	0	0	1
	Hypertensive	3	0	3	3‡
Accidental haemorrhage		2	1	1	0

* The one case of placenta praevia.

† This total includes one case in which histology was unreliable owing to infection. Mild hypertensive changes were almost certainly present.

‡ These 3 cases showed both hypertensive and "renal" changes.

The standards adopted for the categories were as follows:

(1) Normal: Blood pressure never recorded above 120/80 mm. Hg except in labour. No oedema nor albuminuria to which some definite local cause could not be ascribed.

The Caesarean sections undertaken on patients in this group were for a wide variety of obstetrical indications.

(2) Hypertensive: Blood pressure exceeding 120/80 mm. Hg in the non-pregnant state or in the first half of pregnancy.

Patients with a blood pressure consistently or frequently exceeding 160/100 mm. Hg were classified as severe hypertensives. For the purposes of this investigation those patients who were known to have been normotensive before the 20th week but who subsequently developed an elevated blood pressure without oedema and/or albuminuria were regarded as mild hypertensives.

(3) Pre-eclamptic: Blood pressure rising above 120/80 mm. Hg for the first time after the 20th week of pregnancy and in whom such hypertension was accompanied by generalized oedema and/or albuminuria for which no localized cause could be found.

In both the hypertensive and pre-eclamptic groups, the Caesarean section may have been undertaken for this reason alone, or, more frequently, on account of a coexistent obstetrical abnormality.

(4) Eclamptic: In addition to fulfilling the criteria for pre-eclampsia, these patients developed eclamptic convulsions either before or within 24 hours of delivery.

(5) Renal: Cases in which definite impairment of renal function as measured by the usual clinical and biochemical investigations was present. In one case the diagnosis was confirmed by renal biopsy.

This category was further subdivided into those with renal functional impairment alone and those in whom it was complicated by hypertension. All the hysterotomy specimens were obtained from this group and in the whole group operation was undertaken on account of the renal disease.

(6) Accidental Haemorrhage: This condition was classified separately.

RESULTS

(1) *Normotension*

The myometrial vessels, which varied from arterioles to small and medium-sized arteries depending on the depth of the biopsy, usually showed no remarkable histopathological appearances. Due allowance had to be made for parity in assessing fibroelastosis of the intima of the larger vessels, a normal feature of the parous uterus. Occasional small arteries appeared to show medial hyperplasia with stenosis of the lumen, but the special stains revealed no increase of connective tissue in the walls of such

arteries and the impression was gained that this appearance could be explained by spasm.

The decidual arterioles, which were seldom very conspicuous above the level of the spiral arterioles in the basalis, appeared as relatively thin-walled, muscular vessels lined by flattened endothelial cells (Fig. 1).

(2) *Essential Hypertension*

Where the hypertension was mild and uncomplicated by pre-eclampsia only slight changes were discernible. These took the form of hyperplasia of the myometrial arteries in which a definite increase in connective tissue elements of the media, and to a lesser extent the intima, could be detected. Frequently the lumina were stenosed and the endothelial cells swollen and vacuolated suggesting that spasm was an additional factor.

The decidual arterioles, which were now distinctly more prominent, usually showed thickening of their walls accompanied in some instances by a smudgy hyaline appearance. In the one case of severe essential hypertension the spiral arterioles showed very pronounced hyperplastic and hyaline change (Fig. 2). There appeared to be a distinct relationship between the number and severity of the lesions and the degree of hypertension.

(3) and (4) *Pre-eclampsia and Eclampsia*

Mild cases of pre-eclampsia showed changes differing in no obvious way from the pure hypertensive cases but in the more severe cases striking changes were encountered in both the myometrial and decidual vessels.

The myometrial arteries showed advanced medial and intimal hyperplasia with marked increase in connective tissue in the whole vessel wall, gross stenosis (Fig. 3) and, in some cases, complete obliteration of the lumen (Fig. 4). In the most severe cases, with or without eclampsia, intravascular thromboses of varying ages were encountered (Fig. 5).

The changes in the decidual arterioles paralleled those seen in the myometrial vessels. The walls became hyperplastic and hyalinized and the lumina stenosed, fibrinoid necrosis and acute arteritis supervened and intravascular thrombosis with necrosis of the decidua ensued (Figs. 6, 7, 8). Once again the changes observed appeared to vary with the clinical severity of the disease.

(5) *Renal Impairment*

Impairment of renal function appeared to affect the vessels of the placental bed in a distinctive fashion. In all four cases the myometrial and decidual arterioles showed changes which appeared to vary according to the severity of the renal impairment and which could only be interpreted as degenerative in type. Many vessels exhibited a peculiar basophilic, possibly mucoid, degeneration of the media accompanied by proliferative fibrosis and intimal hyperplasia with hydropic vacuolation of the endothelial cells (Fig. 9). The impression that such vessels were degenerate was reinforced by the frequent observation of fibrin deposition in the decidua around the vessels suggesting permeability of the vessel wall to plasma. The mechanism of production of this type of lesion is obscure but it seems reasonable to conclude that it is related in some way to the renal impairment.

Where hypertension or pre-eclampsia coexisted with renal disease the changes described for these conditions were superimposed upon the already damaged vessels (Fig. 10).

(6) *Accidental Haemorrhage*

In one of the cases of accidental haemorrhage vessel changes were seen in both the myometrium and decidua which were interpreted as being due to hypertension or pre-eclampsia. The myometrial vessels appeared hyperplastic, the decidual vessels were prominent and in some cases showed a mild peri-arteritis (Fig. 11). In the other case the vessels were normal.

Discussion

From the results obtained in this series there seems no doubt that organic changes occur in the blood vessels of the placental bed when the course of pregnancy is complicated by systemic hypertension whether the hypertension precedes or arises during the pregnancy. Furthermore it would appear that the extent of these changes is

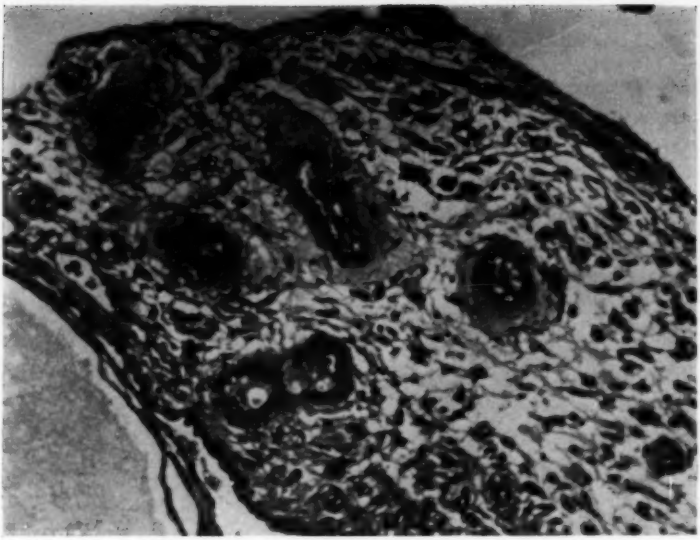


FIG. 1

Normotension. Multigravida. Normal decidual arterioles. H. & E. ×160.

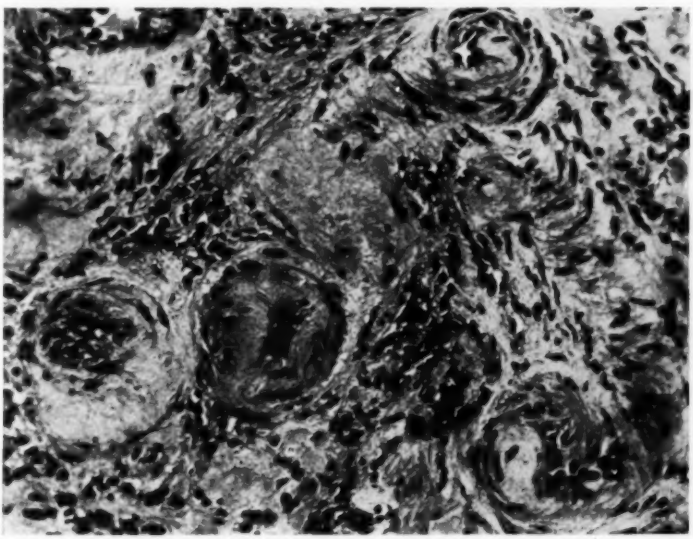


FIG. 2

Essential hypertension. Multigravida. Hyperplastic, hyalinized and stenosed spiral arterioles. H. & E. ×272.

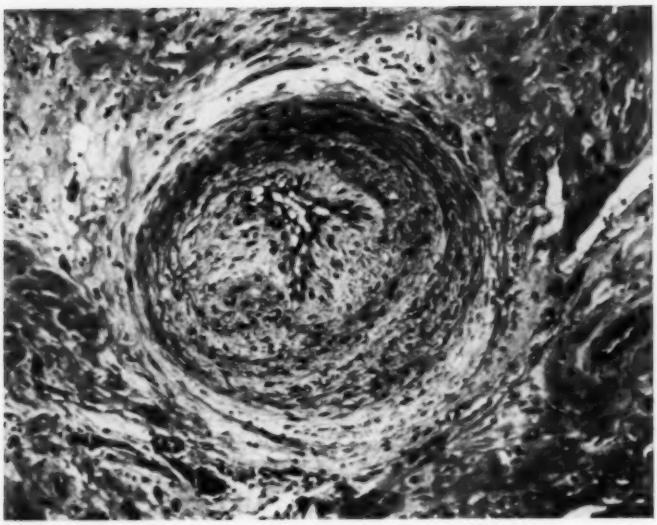


FIG. 3

Essential hypertension with pre-eclampsia. Primigravida. Hyperplastic and grossly stenosed myometrial artery. H. & E. ×128.

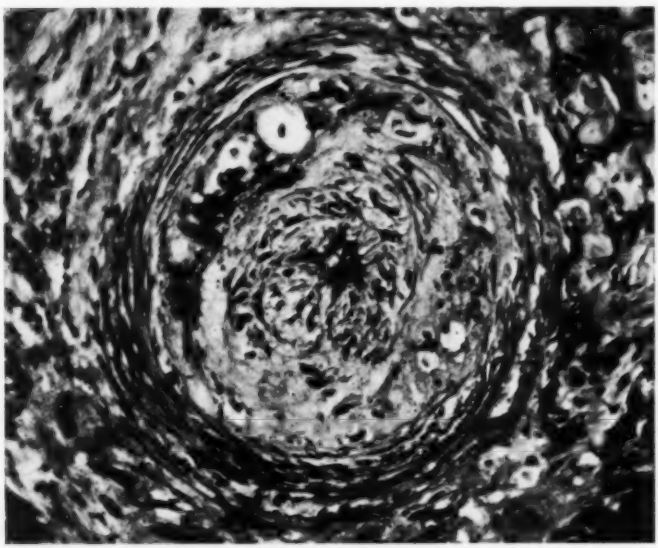


FIG. 4

Essential hypertension with pre-eclampsia. Primigravida. Occlusion of lumen in hyperplastic myometrial artery. M.T. ×272.

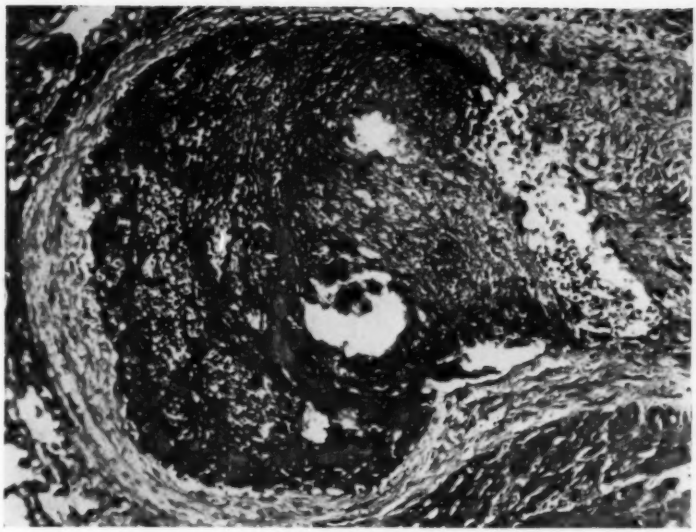


FIG. 5
Severe pre-eclampsia. Multigravida 28-weeks gestation. Organizing mural thrombosis (top, right) with superimposed recent occluding thrombus in myometrial sinusoid. H. & E. ×96.

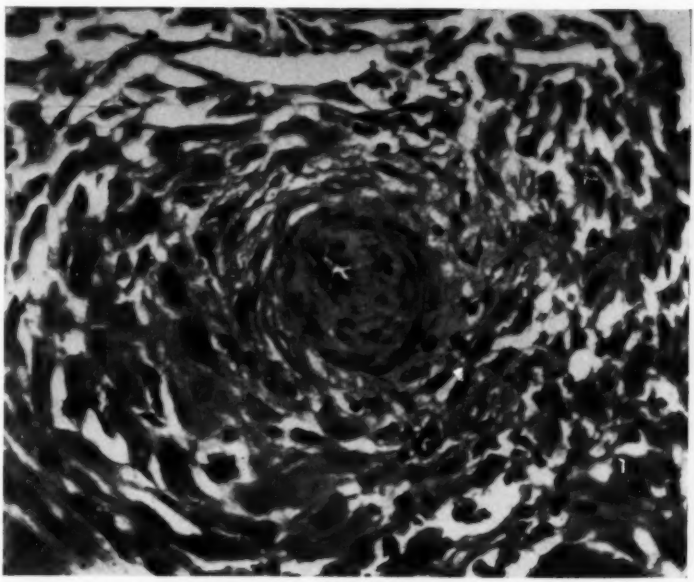


FIG. 6
Essential hypertension with pre-eclampsia. Multigravida. Decidual arteriole showing hyalinized hyperplastic change with stenosis of the lumen. H. & E. ×340.

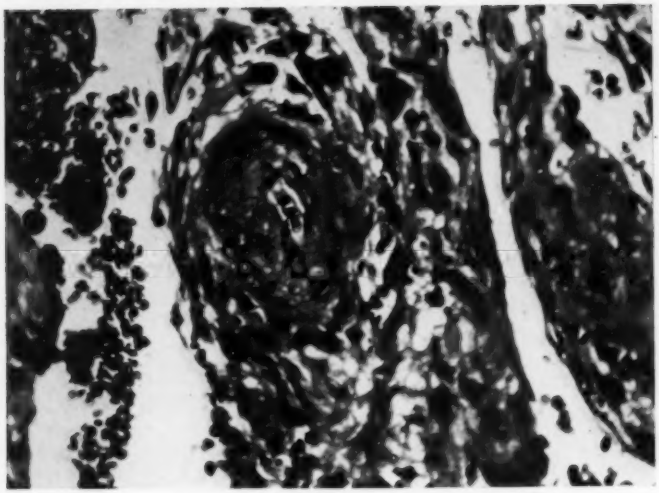


FIG. 7

Essential hypertension with pre-eclampsia. Multigravida. Fibrinoid necrosis of decidual arteriole. H. & E. ×272.

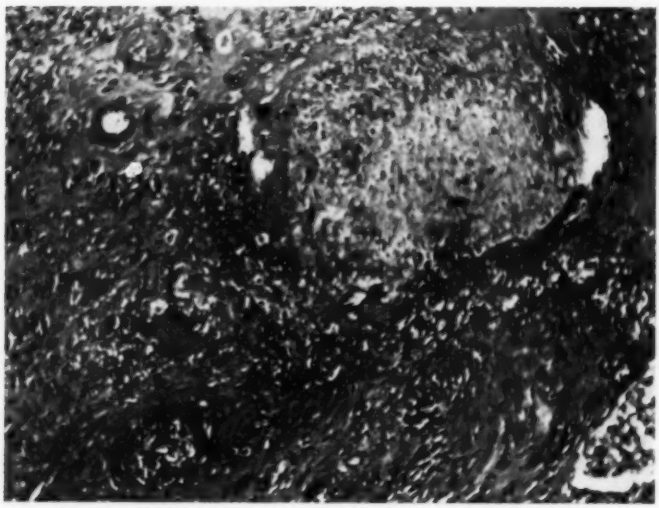


FIG. 8

Severe pre-eclampsia. Multigravida 28-weeks gestation. Fibrinoid degeneration and thrombosis of decidual vessels with infarction of the decidua. H. & E. ×42.

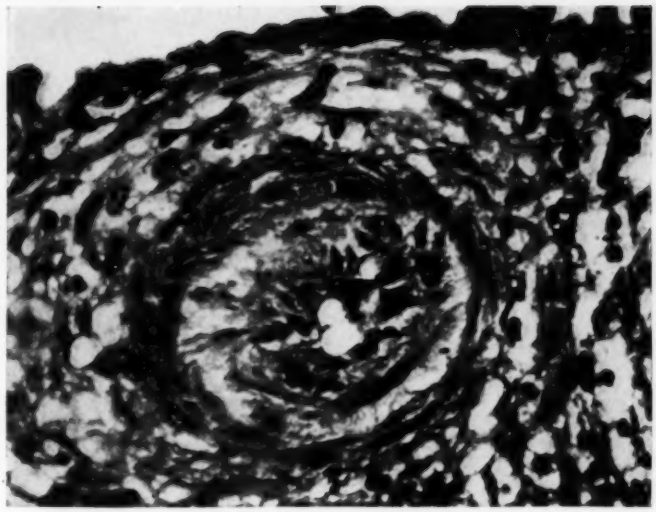


FIG. 9

Normotension with renal impairment. Multigravida 12-weeks gestation. Spiral arteriole showing medial degeneration and intimal proliferation. H. & E. ×525.

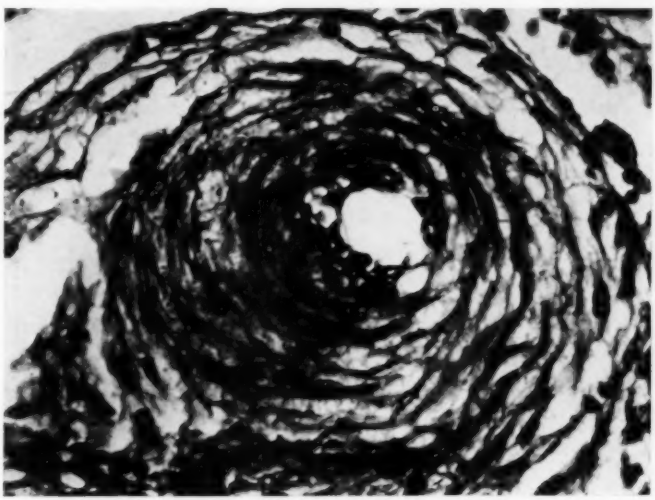


FIG. 10

Renal impairment with hypertension. Multigravida 15-weeks gestation. Hyperplastic decidual arteriole with degenerative change. H. & E. ×480.

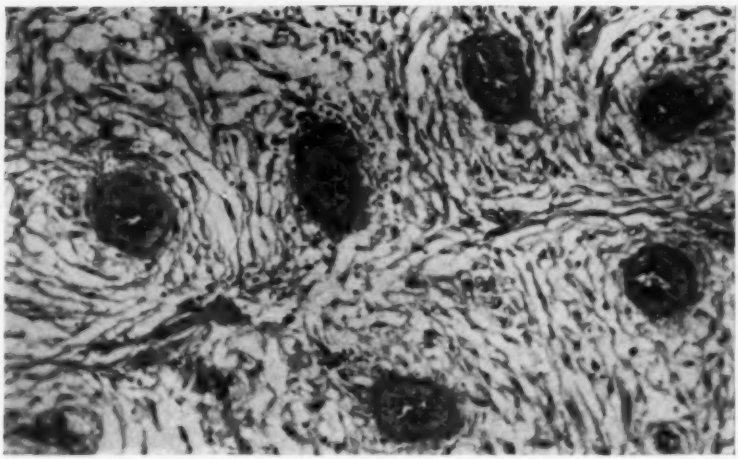


FIG. 11

Accidental haemorrhage (probably toxic). Multigravida. Thickened spiral arterioles with mild peri-arteritis. H. & E. ×24.

FIG. 12

Renal impairment with hypertension. Multigravida 30-weeks gestation. Lipophage infiltration and fibrinoid degeneration of decidual sinusoid. H. & E. ×340.

directly related to the clinical severity of the disease.

All the cases of "mild" essential hypertension fell between the strict criteria of 120/80 mm. Hg suggested by Browne and Browne (1955) and the level of 140/90 mm. Hg adopted by the Royal College of Obstetricians and Gynaecologists and, in these, all gradations from normal to moderate changes were seen in the placental bed vessels. The extent of the changes is related to the level of hypertension attained but in this small series we are unable to detect any critical level for mild hypertension above which changes are invariably present. We would emphasize, however, that whilst no changes were seen in the vessels of the placental bed in normotensive patients with a normally situated placenta, these changes began to appear as soon as the level of 120/80 mm. Hg had been exceeded.

Comment has been made on the site of the placenta, as in the one case of placenta praevia included there were histological vessel changes. These took the form of mild thickening of the myometrial and decidual vessels with some apparent narrowing of the lumina but it was thought that the cause of these appearances might be vessel spasm rather than organic change.

One case of severe essential hypertension who developed pre-eclampsia seems worthy of special comment. She was a primigravid woman of 35, who had been on "Adelphane" therapy for essential hypertension for some months and was still being treated at the time of conception. The therapy was continued throughout pregnancy. In spite of this she developed severe pre-eclampsia at 30 weeks gestation and the changes in her placental bed vessels were amongst the most severe seen (Figs. 3 and 4).

Whilst the changes found in hypertension and pre-eclampsia have been characteristic, we have become aware during this preliminary investigation that other maternal diseases associated with pregnancy may be responsible for vascular lesions in the placental bed. We have already described the lesions found in cases with impaired renal function. The extent of this lesion appears to be related to the degree of renal impairment as measured by the tests available. It is noteworthy that whilst the one patient with renal impairment but a normal blood pressure showed this peculiar change in the vessels of the placental bed at 15 weeks (Fig. 9), those in whom hypertension complicated the renal disease showed the typical changes of hypertension as well as the basic "renal" changes, and in the one such patient treated by termination of pregnancy this picture was observed at 12-weeks gestation (Fig. 10).

The 2 cases of accidental haemorrhage seem of particular interest. One was normotensive by all standards. The haemorrhage was followed by hypofibrinogenaemia and histological examination of the placental bed has failed to reveal any vessel changes whatsoever. The other patient was known to have been hypertensive during a previous pregnancy when her blood pressure was 155/90 mm. Hg on booking at 25 weeks. At 29 weeks the recorded level was 175/110 mm. Hg. In spite of admission to hospital and treatment she developed an accidental haemorrhage. Two months after this delivery her blood pressure was recorded as 130/95 mm. Hg. During the present pregnancy the blood pressure remained normal from the 12th to the 37th week. At 38 weeks she was admitted with a clinical accidental haemorrhage, slightly shocked and with a blood pressure of 130/90 mm. Hg. There was no albuminuria nor oedema. Caesarean section was undertaken in the hope of saving the baby but it died some 18 hours after delivery. Post-mortem examination showed the cause of death to be asphyxia with gross inhalation of meconium. After delivery the maternal blood pressure oscillated between 140/90 mm. Hg and 150/100 mm. Hg but by the sixth week after delivery it was 110/65 mm. Hg. We are thus unable to say with any certainty whether this was a "toxic" accidental haemorrhage or not, but there seems sufficient presumptive evidence to classify it as such. The placental bed biopsy showed definite organic changes in the myometrial and decidual arterioles which were interpreted as being due to hypertension (Fig. 11).

The nature of the lesions we have observed and illustrated in the vessels of the myometrium and decidua requires some comment as a fairly clear picture of their natural history emerges from a study of the cases in order of severity.

With the onset of hypertension, even of a relatively mild degree, hyperplastic changes appear first in the media and later in the intima. This may be followed by a greater or lesser degree of hyaline change depending on the duration and severity of the hypertension. When the hypertension becomes more severe, and especially when its onset is sudden and its progression rapid, acute degenerative changes in the form of fibrinoid necrosis, acute arteritis and intravascular thrombosis become evident. The degenerate vessels allow diffusion of plasma through their walls with consequent deposition of fibrin in and around the vessels.

The arteriolar damage, as one might expect, causes necrosis and infarction of the decidua which frequently involves the large, thin-walled and fragile decidual sinusoids leading to haemorrhage or further infarction. The damage to the maternal vessels consequent upon hypertension affords a simple explanation of retroplacental haemorrhage and placental infarction which at the same time is in keeping with the general principles of pathology. That this is so was suggested by Dieckmann (1936) in his studies of abruptio placentae.

It is generally accepted that the changes observed in arteries and arterioles in systemic hypertension, both benign and malignant, are the result and not the cause of the hypertension We have demonstrated identical lesions in the vessels of the placental bed in hypertensive and pre-eclamptic pregnancy and it must be concluded that these changes are also secondary to the hypertension. They appear to develop more rapidly and to be of greater severity than would be expected in non-pregnant women with hypertension of a similar degree and duration. It seems that in pregnancy the vessels of the uterus, at least those of the placental bed, are more susceptible to the effects of hypertension than vessels elsewhere in the body and those in the non-pregnant hypertensive subject. The reason for this may be related to the physiological hyperplasia of the uterus in pregnancy and to the probability that the new vessels developing in the decidua are less able to withstand increased pressure than long established and less precariously placed vessels outside the uterus.

Our findings do not substantiate the occurrence of a specific lesion in the decidual vessels as has been suggested by Hertig (1945) and Zeek and Assali (1950) who describe an "acute atherosis", characterized by the infiltration of the intima of the vessels by lipophages with subsequent fibrinoid necrosis and arteritis. Indeed, Hertig (Sexton *et al.*, 1950) now considers that this lesion is only seen in toxaemic cases complicated by essential hypertension or chronic nephritis and has suggested that arteriolar spasm is the operative factor in purely toxaemic subjects. We have observed such lesions (Fig. 12) but it is our opinion that they are commoner in venules and sinusoids than in arterioles and we agree with the view of Burnstein, Blumenthal and Soule (1957) that they are probably of a secondary nature. As pointed out by these authors there is no known example in general pathology of an acute inflammatory vasculitis with an atheromatous element. A picture analogous to "acute atherosis" is frequently seen in the vessels of the brain in and around old cerebral softenings where lipophages abound and, where there is necrosis of the decidua as there certainly is in severe cases of hypertension with toxaemia, one must expect the liberation and phagocytosis of lipoid material. This point requires investigation by frozen section techniques which the standard method of processing our material for this study precluded.

We feel that there is no necessity to depart from the generally accepted principles of vascular pathology to explain the lesions in the placental bed. They are the characteristic result of hypertension. In view of the similarity of the changes found in the presence of essential hypertension and pre-eclampsia it does not seem reasonable that what is postulated as effect in the one case should be put forward as cause in the other.

Owing to our findings in the cases of renal impairment we do not wish to imply that hypertension is the only maternal abnormality which is capable of producing vascular changes in the placental bed.

We consider that the maternal hypertension and consequent vessel changes afford an adequate explanation for the reduction of chorio-

decidual blood flow observed in both essential hypertension and pre-eclampsia, and furthermore, that they offer a satisfactory explanation for the placental degeneration and the hazard to the foetus present in these conditions.

Summary

(1) Biopsies of the placental bed have been taken from 36 patients. Histological examination has been carried out with particular reference to pathological changes in the maternal vessels and these changes have been related to the clinical histories of the patients.

(2) Vascular lesions have been found in material obtained from hypertensive and from toxaemic women. These changes are in no way distinguishable from those generally acknowledged to occur as a result of systemic hypertension. They are directly related in extent to the clinical severity of the disease.

(3) No such changes have been found in normal patients.

(4) Apart from differences of degree, the vessel changes in essential hypertension and pre-eclampsia appear identical. They are thought to be due to hypertension.

Acknowledgments

We wish to thank the consultant and registrar staff of the Division of Obstetrics and Gynaecology of the University College Hospital of the West Indies for their co-operation. We are especially indebted to Professor D. B. Stewart for his encouragement and advice. Our thanks are also due to Miss O. C. Dawes and Mr. L. Edwards of the Department of Pathology for their invaluable technical and photographic assistance.

References

Assali, N. S., Douglass, R. A., Baird, W. W., Nicholson, D. B., and Suyemoto, R. (1953): *Amer. J. Obstet. Gynec.*, **66**, 248.

Bartholomew, R. A., Colvin, E. D., Grimes, W. H., Fish, J. S., Lester, W. M., and Galloway, W. H. (1957): *Amer. J. Obstet. Gynec.*, **74**, 64.

Bastiaanse, M. A. van B., and Mastboom, J. L. (1949): *Ned. Tijdschr. Geneesk.*, **93**, 2609.

Browne, F. J., and Browne, J. C. McClure (1955): *Antenatal and Postnatal Care*. 8th edition. Churchill, London. p. 373.

Browne, J. C. McClure (1957): Personal communication.

Browne, J. C. McClure and Veall, N. (1953): *J. Obstet. Gynaec. Brit. Emp.*, **60**, 141.

Burnstein, M. D., Blumenthal, H. T., and Soule, S. D. (1957): *Amer. J. Obstet. Gynec.*, **74**, 85.

Colvin, E., and Bartholomew, R. A. (1938): *Amer. J. Obstet. Gynec.*, **36**, 909.

Dieckmann, W. J. (1936): *Amer. J. Obstet. Gynec.*, **31**, 734.

Hertig, A. T. (1945): *Clinics*, **4**, 602.

Johnson, T., and Clayton, C. G. (1957): *Brit. med. J.*, **1**, 312.

Metcalfe, J., Romney, S. L., Ramsey, L. H., Reid, D. E., and Burwell, C. S. (1955): *J. clin. Invest.*, **34**, 1632.

Morris, N. (1957): Personal communication.

Morris, N., Osborn, S. B., and Wright, H. P. (1955): *Lancet*, **1**, 323.

Ogden, E., Hildebrand, G. J., and Page, E. W. (1940): *Proc. Soc. exp. Biol., N.Y.*, **43**, 49.

Page, E. W. (1948): *Obstet. Gynec. Surv.*, **3**, 615.

Russell, C. S., Paine, C. G., Coyle, M. G., and Dewhurst, C. J. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 649.

Sexton, L. I., Hertig, A. T., Reid, D. E., Kellogg, F. S., and Patterson, W. S. (1950): *Amer. J. Obstet. Gynec.*, **59**, 13.

Tenney, B., Jr. (1936): *Amer. J. Obstet. Gynec.*, **31**, 1024.

Thompson, R. H. S., and Tickner, A. (1949): *Biochem. J.*, **45**, 125.

Young, J. (1914): *J. Obstet. Gynaec. Brit. Emp.*, **26**, 1.

Zeek, P. M., and Assali, N. S. (1950): *Amer. J. clin. Path.*, **20**, 1099.

A CASE OF CHRONIC INVERSION OF THE UTERUS

BY

C. JOHN MACKINLAY, *T.D.*, M.D., M.R.C.O.G.

The Royal Samaritan Hospital for Women, Glasgow

CHRONIC inversion of the uterus without an obvious cause is so rare that the following case seems worthy of reporting.

The patient was admitted urgently on account of severe vaginal bleeding. She was 79 years of age, had had 9 children and gave a history of having had a repair operation for prolapse 5 years previously. She was found to be a poor old woman, emaciated and dirty. She came from a condemned house to which she had been confined for the past year, unable to move far because of the swelling between her legs. The swelling was about 12 cm. in diameter, it was raw, infected and bleeding and was attached to a completely prolapsed and distended vagina. At first glance the tumour was thought to be a sloughing fibroid polypus or a carcinoma of the cervix but on closer examination it was found to be a completely inverted uterus.

Warm antiseptic swabs were applied to the uterus and the whole swelling was reduced within the vulva and held in place by packing. It was not possible, however, to reduce the inversion of the uterus. The relief to the patient was considerable and the bleeding stopped. On the day after admission the patient's condition was so poor that it did not seem possible that one would ever be able to operate upon her, but it appeared that the patient was literally starving and the improvement in 10 days with plenty to eat was remarkable.

She was taken to the theatre on the 10th day after admission (Fig. 1). The uterus still bled to the touch but it was greatly reduced in size and was comparatively healthy. A vaginal hysterectomy was performed and the cystocele and enterocele were repaired. She made an uninterrupted recovery and stated when she was being dismissed 3 weeks later that she had never felt so well in her life.

DISCUSSION

An interesting feature of this case is that there was no obvious reason why the uterus should have become inverted. The cervix had been partially amputated during the repair operation 5 years previously but the remainder of the cervix gripped the uterus so tightly that reduction of the inversion was quite impossible. There was no fibroid or polypus which might have started the inversion process.

I have been able to trace 4 cases of chronic inversion of the uterus in this hospital over a period of 30 years but none was similar to the case described.

Two patients, aged 39 and 40, had inversion of the uterus associated with large submucous fibroids, one patient aged 54 had a partial inversion associated with a small submucous fibroid and one patient, aged 26, was a puerperal case, the condition being discovered 2 months after the birth of her first child. Three of these patients had the uterus replaced without much difficulty, but in the case of the patient aged 54, an abdominal hysterectomy was performed.

During the 30 years in which these 5 cases occurred there were over 100,000 admissions to the hospital.

SUMMARY

A case of chronic inversion of the uterus of unknown origin in a woman aged 79 years is described.

1 Pl.

FIG. 1

The completely inverted uterus is held upwards. A length of silk has been inserted into the orifice of each tube. The enterocele can be seen posteriorly.

PREGNANCY IN ASSOCIATION WITH CROHN'S DISEASE

BY

R. LLOYD JONES, M.B., F.R.C.S., M.R.C.O.G.
Leverhulme Research Scholar
Institute of Clinical Research, The Middlesex Hospital, W.1

AND

D. H. K. SOLTAU, M.A., M.B., F.R.C.S., M.R.C.O.G.
Obstetric and Gynaecological Registrar
The Middlesex Hospital, W.1

IN 1932 Burrill Crohn and his colleagues (Crohn, Ginzburg and Oppenheimer) described the entity now called by his name; several series of cases have been reported since, and the numerous complications are well recognized. There are, however, few reports on the association of pregnancy with the disease.

We have studied the records of 36 cases of Crohn's disease in women treated at the Middlesex Hospital during the period of 1945–1955; in 2 of these cases pregnancy followed the disease, while in 3 cases it was associated with active Crohn's disease. Four of the 5 patients were confined in this hospital and their case histories illustrate some of the ways in which regional ileitis may influence pregnancy, and affect the obstetric management.

CASE REPORTS

Case 1

Mrs. M.M., aged 40, gave the following history.

Her general health had been good until November, 1941, when she was admitted to another hospital with a diagnosis of acute appendicitis. An acutely inflamed appendix was removed soon after admission. Convalescence was uneventful until the 4th day when she developed a swinging temperature associated with increasing abdominal distension. On the 10th day laparotomy was performed and an anastomosis made between what appeared to be the lower jejunum and the upper ileum.

As this did not relieve the obstruction an ileostomy was performed on the 12th day. Her condition improved gradually and the ileostomy closed spontaneously. She was discharged after two months in hospital, but complained of great lassitude, loss of 2 stones (12·6 kg.) in weight, persistent diarrhoea, occasional soreness of the mouth and oedema of the legs and ankles. Her menstruation, previously regular, ceased after the operation, and she complained of infertility. These symptoms are typical of chronic jejuno-ileal insufficiency associated with an internal fistula, as described by Izod Bennett and Hardwick (1940).

In June, 1949, as her health was no better, she attended the surgical out-patient department at the Middlesex Hospital. Barium meal and barium enema studies showed the presence of a fistula between the upper jejunum and the transverse colon, presumably the anastomosis performed in 1941. It was apparent that the diarrhoea was due to this short-circuiting of a major part of her intestine, and it was decided to attempt a reconstruction of the normal anatomy.

Laparotomy was performed on 16th September, 1949, by Mr. R. S. Handley. Exploration showed that the terminal ileum was distended and the caecal wall thickened. The jejuno-transverse colostomy was undone, and a right hemi-colectomy performed. Histological examination of this specimen showed that the bowel was the site of active Crohn's disease. Her general health improved greatly after this operation, and she gained 4 stones (25·2 kg.) in weight within 6 months. Regular menstruation began spontaneously after 3 months, and she became pregnant for the first time in September, 1950, one year after the operation.

In June, 1951, she was delivered of a healthy infant weighing 8¼ pounds (3,856 g.) by Caesarean section, because she was an elderly primigravida and the presentation was by the breech. The puerperium was uneventful and breast feeding was satisfactory.

She attended again in July, 1954, pregnant for the second time. At this and subsequent visits it was noted that she remained very well, with no diarrhoea and no evidence of the mal-absorption syndrome. Pregnancy was normal throughout, and, in the absence of any obstetric complications, she had a normal vaginal delivery of a healthy infant weighing 7 pounds 1½ ounces (3,387 g.), which was breast fed.

Case 2

This was an example of the mal-absorption syndrome with tetany, which followed extensive resection of a congenitally short small intestine.

This syndrome may be produced either by changes in the mucous membrane of the small gut leading to inefficient absorption, or by an insufficient length of functioning gut remaining after resection. Both these factors may be present in cases of Crohn's disease.

Mrs. J.C., aged 24, had a long history of dyspepsia and minor attacks of abdominal pain. She was admitted to hospital with chronic intestinal obstruction in February, 1953, under the care of Mr. R. Vaughan Hudson. Laparotomy was performed, disclosing multiple strictures of the jejunum and ileum due to Crohn's disease, so that it was necessary to remove approximately 5 feet (150 cm.) of affected small intestine. She was noted to have a congenitally short intestine, so that after resection only about 5 feet (150 cm.) of small bowel remained. Her immediate post-operative progress was satisfactory, but 2 to 3 months later she developed tetany due to insufficient absorption of calcium. These symptoms became worse, and in May, 1954, she was re-admitted to hospital for investigation of this mal-absorption syndrome.

At that time, before treatment, the serum calcium level was 7·1 mg. per 100 ml., with phosphate 4·5 mg. per 100 ml. The serum proteins were 6·0 g. per 100 ml. (albumin 2·8 g., globulin 3·2 g.: an almost complete reversal of the normal ratio). She was treated with 100,000 units of Calciferol and 45 grains (3·0 g.) of calcium gluconate daily, together with a high protein diet.

Two weeks later, after treatment, the serum calcium had risen to 9·3 mg. per 100 ml., with phosphate 4·1 mg. per 100 ml. The serum proteins were 6·2 g. per 100 ml. (albumin 3·2 g. and globulin 3·0 g.). The treatment was continued and subsequently her general health remained good.

She then became pregnant and attended the antenatal clinic in September, 1954, when she was 7-weeks pregnant.

Her general condition was satisfactory, and her usual dosage of calciferol and calcium gluconate was maintained throughout pregnancy.

It has been found by several workers that the serum calcium level is lowered slightly in pregnancy, though seldom below 8·8 mg. per 100 ml. (Mull and Bill, 1934; Clayton and Oram, 1951). It has been suggested that this slight fall in the calcium concentration is due to the dilution of the plasma in pregnancy. In this case the serum calcium did not fall below 9·3 mg. per 100 ml.

It was not found necessary to increase the dosage of calciferol or calcium gluconate during pregnancy, and the patient was not noted to complain of muscular cramps or other possible manifestations of calcium deficiency. Labour began at term, and she was delivered by forceps of a healthy infant weighing 6 pounds 1 ounce (2,750 g.).

Negative calcium balances are frequently found during lactation, even with a good dietary intake (Duckworth and Warnock, 1942), so it was considered unwise to allow breast feeding. Lactation was therefore suppressed and artificial feeding was instituted. The serum calcium level on the 10th day of the puerperium was 9·2 mg. per 100 ml.

She remained well after this, and became pregnant again in 1956. Pregnancy was normal throughout; she was delivered at term of an infant weighing 6 pounds 10 ounces.

The same dosage of calciferol and calcium gluconate was continued, and again she remained symptom-free. The serum-calcium level ranged from 7·8 to 9·4 mg. per 100 ml.

Case 3

Mrs. S.H., aged 27, had an ischio-rectal abscess incised in June, 1949. Two months later she was admitted to this hospital and found to have a high-level fistula-in-ano. This was operated upon by Mr. D. H. Patey.

In 1951 she complained of intermittent, colicky, abdominal pain, diarrhoea and a general feeling of lethargy. An indefinite tumour could be felt in the right iliac fossa; a barium meal showed radiological appearances compatible with Crohn's disease in the terminal ileum. As the inflammatory process did not subside under expectant treatment, she was re-admitted to hospital in March, 1952, and an ileo-transverse colostomy with exclusion of the terminal ileum was performed. The terminal 8 inches (20 cm.) of ileum were thickened and indurated, with the changes typical of Crohn's disease. The rest of the small and large intestine was normal; the small intestine was approximately 12 feet (3·6 m.) in length. Her post-operative progress was uneventful, though she still complained of some diarrhoea.

In August, 1952, she attended the clinic and was found to be 6-weeks pregnant. At this time the diarrhoea and lower abdominal pains became more troublesome; she was treated with banthine, 50 mg. b.d. and *mist. cret. cum opio* with considerable relief. Apart from these symptoms the pregnancy progressed normally, and it was decided that, in spite of her extensive perineal scarring, vaginal delivery was justifiable provided that an episiotomy was performed. Labour began at term, and after episiotomy an easy outlet forceps delivery was effected after 7½ hours; the infant weighed 6 pounds 5 ounces (2,860 g.). The puerperium was uneventful and breast feeding was established satisfactorily.

Following this pregnancy her symptoms of diarrhoea and lower abdominal discomfort remained unchanged, and when seen in November, 1955, these were relieved by probanthine 15 mg. b.d.

Barium meal examination in June, 1956, showed evidence of Crohn's disease in the ileum proximal to the anastomosis. It was decided to continue with expectant treatment.

She then became pregnant. Her pregnancy was normal and she was delivered normally after episiotomy.

During her pregnancy, the abdominal symptoms remained more or less unchanged, until about a month after delivery, when there was a slight exacerbation of abdominal pain and diarrhoea. This persisted for about 6 months, when she returned to her previous state.

This was an example of normal pregnancy in the presence of Crohn's disease which had received previous surgical treatment, and which showed some evidence of reactivation during and after pregnancy, though this was not severe.

Case 4

Mrs. V.B., aged 32, underwent an operation for fistula-in-ano in 1943. In 1948 she was referred to Mr. D. H. Patey at this hospital with a history of chronic diarrhoea of 3-years duration. In 1946 she had a normal pregnancy and labour which did not appear to have aggravated her symptoms.

After investigation a diagnosis of Crohn's disease was made, and an ileo-transverse colostomy with exclusion of the terminal ileum was performed. In 1951 she became pregnant for the second time; during this pregnancy she complained of flatulence and diarrhoea. She was delivered normally at term.

In February, 1952, 2 months after the confinement, her symptoms became worse and she was found to have a rectal stricture. She was re-admitted to hospital in June, 1952, for dilatation of the stricture and sigmoidoscopy; dilatation was continued thereafter in the outpatient department. However there was no improvement in her condition, and in June, 1953, a left iliac colostomy was established. A year later symptoms recurred, with the passage of blood, pus, and mucus from the colostomy. X-ray investigation showed the presence of diseased bowel between the colostomy and the ileo-transverse colostomy. A trial of chemotherapy gave only temporary benefit, so an ileostomy was performed in 1954, after which she made good progress until September, 1955, when there was a further recurrence of symptoms. In November, 1955, subtotal colectomy was performed, the blind ileal stump and the colon down to the colostomy being removed.

In this case there was no deterioration noted after the first pregnancy, but the patient's symptoms increased in severity so much after the second confinement that this may well have been an exciting factor.

Case 5

Mrs. P.G., aged 29. This patient's general health had always been good, with no serious illnesses or operations, and her first pregnancy in 1950 was uneventful, ending in a forceps delivery at term of a healthy infant weighing 5 pounds 6 ounces (2,442 g.).

In August, 1954, she attended again, 8-weeks pregnant, and complained of excessive flatulent dyspepsia of recent origin. A barium meal examination excluded any abnormality of the stomach and duodenum; there was no hiatus hernia. Her health was otherwise good; there was no diarrhoea and no evidence of anaemia. She attended her local clinic for antenatal examinations until the 36th week of pregnancy. When seen at that time her only complaint was of heartburn.

At 37-weeks she was admitted to hospital as an emergency, complaining of intermittent, mild, lower abdominal pain of 3-days duration. The pain was ill-defined but somewhat worse in the right iliac fossa; she had not vomited.

On admission her general condition was good, with normal temperature and pulse rate. Her tongue was clean, there was no abdominal tenderness or guarding, and rectal examination did not reveal any abnormality. Obstetric examination was completely normal, and she was having irregular uterine contractions. A diagnosis of acute appendicitis appeared to have been excluded by these findings.

The following morning she was distressed by her pain, particularly on moving, and some generalized abdominal tenderness became apparent, but her temperature and pulse rate still remained normal. She was then in labour.

During the day labour progressed normally and there was no vomiting, although she complained of intermittent pain in the right iliac fossa. She was delivered spontaneously of a healthy infant weighing 5 pounds 10 ounces (2,556 g.) after a labour lasting 30 hours. Throughout labour her general condition remained satisfactory, her maximal pulse rate being 96. Only 200 mg. of pethidine were required to relieve her pain.

On the first day of the puerperium she complained again of mild, intermittent pain which did not distress her and was relieved by codeine, the temperature and pulse rate remaining normal. By the evening the temperature had risen to 100° F., with a pulse rate of 100. By this time minimal abdominal distension was apparent, with some tenderness on palpation but without guarding or rigidity. Because bowel sounds could not be heard on auscultation it was decided to treat her expectantly, with gastric suction and intravenous fluids.

The next day she felt better, though still complaining of pain; bowel sounds had returned and gastric aspiration was discontinued. The leucocyte count at this time was 5,300 per c.mm., with 69 per cent neutrophils.

Her general condition improved for 2 days, but thereafter she developed a swinging temperature followed by mucous diarrhoea. At this stage, 5 days after her confinement, a tumour could be felt in the right iliac fossa for the first time. It was separate from the uterus, which appeared to be involuting normally. The leucocyte count was now 18,900 per c.mm., with 84 per cent neutrophils.

A provisional diagnosis of appendix-abscess was made and laparotomy performed.

On opening the abdomen by a lower paramedian incision, blood-stained free fluid in the peritoneal cavity and an abscess in the right iliac fossa were found. The abscess contained foul-smelling pus; omentum, caecum, the right ovary and the appendix were involved in its wall. The appendix appeared normal at its proximal end, the distal end being involved in the abscess. Appendicectomy was performed and a drain inserted into the abscess cavity. A course of penicillin and streptomycin was commenced.

Following this operation her condition remained satisfactory for 14 hours when she suddenly collapsed, and died after 11 hours with peripheral circulatory failure, in spite of attempted resuscitation with blood-transfusion and l-noradrenaline drip.

Post-mortem examination showed generalized, acute, purulent peritonitis. The terminal ileum was found to show the changes characteristic of subacute regional ileitis, with a perforation of the diseased bowel which communicated with the abscess cavity. There were toxic changes in all viscera, and bilateral basal pulmonary collapse.

In retrospect the sequence of events would seem to have been as follows. The probable duration of active Crohn's disease was a few months only, the patient not complaining of dyspepsia until early in pregnancy. The perforation of the terminal ileum must have occurred just before or at the onset of labour, with subsequent partial localization of infection and abscess formation.

During labour and in the puerperium the clinical picture was confusing, but at no time did the patient's condition suggest a generalized peritonitis. There was no marked rise in pulse-rate; the slight, temporary, abdominal distension after delivery was no more than that often seen in a recently delivered woman; abdominal tenderness was elicited at times, but there was no guarding or rigidity.

Although the inflammatory mass could not be felt until the 5th day of the puerperium, it might well have been palpable earlier but for the patient's obesity and the presence of the puerperal uterus. The diagnosis of appendicitis was considered repeatedly by several observers, but was not supported by the physical signs, and, until the development of the mass, there did not appear to be a clear indication for operative interference.

Such perforation and abscess formation due to Crohn's disease is a most unusual complication of pregnancy.

Williams and Davis (1946) reported the case of a primigravida aged 23 who complained of abdominal pain at the 33rd week of pregnancy. She had complained of attacks of pain with dyspepsia and fever since the 28th week of pregnancy. Spontaneous premature labour occurred 4 days after admission, with delivery of a healthy infant which survived. On the 3rd day of the puerperium the patient developed pyrexia, and 2 days later a swelling became apparent in the right iliac fossa. Laparotomy was undertaken 18 days later, and revealed oedema of the terminal ileum with fistulous tracks leading into a firm indurated mass extending retroperitoneally. Ten inches of terminal ileum with the caecum and 6 inches of ascending colon were resected, and the patient made a satisfactory recovery after a stormy convalescence. Histological examination of the specimen showed regional ileitis.

Babson (1946) reported a case of regional ileitis with acute intestinal obstruction in the 7th month of pregnancy in a primigravida aged 25. Symptoms of diarrhoea, vomiting, and fever had been present for 2 months previously, with a history of colitis 6 years before.

At operation a large inflammatory mass involving the terminal ileum was found. There was a fistula with an abscess cavity and adjacent peritonitis. An ileo-transverse colostomy was performed, and 10 days later labour began, terminating with the delivery of a premature infant which survived for a few hours.

After a convalescence complicated by a pelvic abscess, evacuated *per vaginam*, the patient made an uneventful recovery. In this case pregnancy appeared to aggravate the patient's symptoms.

These two cases are the only ones we have been able to find reported which are similar to our case.

Comment

The co-existence of Crohn's disease and pregnancy is uncommon, and it is difficult to draw definite conclusions on the effect of pregnancy in the disease by study of small numbers of cases. The chronic stage may last for many years, and the acute exacerbations are separated by long or short periods of good health. Any aggravation or amelioration of symptoms related to pregnancy may well be purely coincidental.

Two of our cases showed an exacerbation of symptoms during and shortly after pregnancy, but in both patients this was slight and temporary.

Bennett and Hardwick (1940), in their discussion of jejuno-ileal insufficiency, stressed that it may be associated with sterility, but that if pregnancy occurred it often produced an acute exacerbation of symptoms.

In 1948 Raffensperger reported the case of a 22-year-old woman who became pregnant 3 months after an ileo-transverse colostomy had been performed for terminal ileitis. The course of her pregnancy was uneventful until the 7th month when she went into labour prematurely. After 2½ months she suffered an acute exacerbation of the regional ileitis. Raffensperger considered that "serious consideration should be given to the possible deleterious effect of pregnancy in similar cases".

In 1949 Crohn cited his experience with one case of ileitis beginning during pregnancy and 5 cases beginning in the post-partum period. He also described 5 cases with uneventful pregnancies after successful surgical intervention for regional ileitis. It was his impression that patients with regional ileitis tolerate pregnancy better than those with ulcerative colitis.

Heard and John (1956) describe a case of regional ileitis in which there was a definite amelioration of symptoms during pregnancy, with a marked exacerbation soon afterwards.

In 1956, Crohn, Yarnis and Korelitz, presented a study of 84 pregnancies in 53 patients who had regional ileitis. In general the pregnancy exerted an unfavourable effect upon the disease, particularly when the ileitis was active at the time of conception. Crohn considers that when ileitis occurs for the first time during pregnancy the course of the disease is likely to be severe; but when it occurs as a post-partum manifestation it is likely to be mild.

We do not feel that there is conclusive evidence of a serious deleterious effect of pregnancy in this disease. Termination of pregnancy is not indicated, even in the presence of active disease.

When Crohn's disease occurs for the first time during pregnancy the diagnosis may be difficult to establish. In the early weeks the symptoms may be regarded as the usual nausea and dyspepsia, while later they may be confused with the dyspepsia due to hiatus hernia. Persistent diarrhoea and abdominal pain should suggest the possibility of Crohn's disease.

In the rare case presenting as an acute abdominal emergency during pregnancy it is unlikely that a correct pre-operative diagnosis can be made, unless there is a suggestive history preceding the acute attack.

The obstetrician is more likely to encounter chronic Crohn's disease which has received surgical treatment. In these cases there may be mal-absorption with hypoproteinaemia, anaemia and calcium deficiency, and the added nutritional demands of pregnancy may necessitate increased dietary supplements.

Watson, Cameron and Witts (1948) commented on the association of macrocytic anaemia with gross intestinal disease, and showed experimentally that such an anaemia could be produced in rats by the formation of a partially closed loop of intestine which becomes distended with intestinal contents. This state of affairs may be present in cases of Crohn's disease after a short-circuit operation. As the anaemia is not usually of a simple hypochromic type the patients will require full haematological investigation before treatment.

In cases which have shown signs of calcium deficiency before pregnancy the further fall in blood calcium level may necessitate increased dosage of calcium and calciferol during pregnancy, and particularly in the puerperium.

Patients with active disease may require gastro-intestinal sedatives and antispasmodics for control of their symptoms.

Summary

(1) Five cases of Crohn's disease associated with pregnancy are described.

(2) These cases illustrate some of the ways in which the disease may influence pregnancy and affect obstetric management.

(3) A fatal case of Crohn's disease with intestinal perforation during pregnancy, is recorded.

We wish to thank those members of the Consultant Staff of the Middlesex Hospital who have given us permission to publish these cases and help in the preparation of this paper, and the staffs of the Courtauld and Bland-Sutton Institutes for carrying out the biochemical and pathological investigations.

References

Babson, W. W. (1946): *New Engl. J. Med.*, **235**, 544.
Bennett, T. I., and Hardwick, C. (1940): *Lancet*, **2**, 381.
Clayton, S. G., and Oram, S. (1951): *Medical disorders in pregnancy*. Churchill, London. p. 25.

Crohn, B. B. (1949): *Regional ileitis*. Grune & Stratton, New York. p. 86.
Crohn, B. B., Ginzberg, L., and Oppenheimer, G. D. (1932): *J. Amer. med. Ass.*, **99**, 1323.
Crohn, B. B., Yarnis, H., and Korelitz, B. I. (1956): *Gastroenterology*, **31**, 615.
Duckworth, J., and Warnock, H. (1942): *Nutr. Abstr. Rev.*, **12**, 167.
Heard, G. E., and John, E. L. (1956): *Brit. med. J.*, **2**, 85.
Mull, J. W., and Bill, A. H. (1934): *Amer. J. Obstet. Gynec.*, **27**, 510.
Raffensperger, E. C. (1948): *Gastroenterology*, **10**, 1010.
Watson, G. M., Cameron, D. G., and Witts, L. J. (1948): *Lancet*, **2**, 404.
Williams, D. L., and Davis, D. R. (1946): *Sth. Surg.*, **12**, 342.

A CASE OF MASSIVE ENDOMETRIAL HYPERPLASIA ASSOCIATED WITH PROLONGED STILBOESTROL ADMINISTRATION

BY

DEREK TACCHI, M.B., M.R.C.O.G.

Senior Registrar

Department of Obstetrics, Newcastle General Hospital, Newcastle upon Tyne

IN the last quarter of a century many powerful therapeutic agents have become available for the treatment of disease. In many instances therapy results in complete cure but occasionally misguided treatment, often given unwittingly, may produce a serious disorder. In the case of Stilboestrol, its relative low cost and ease of administration have made its general use promiscuous (Gusberg, 1947). The following case report illustrates the dangers of such therapy allowed to continue for a prolonged period of time and is of interest because of the enormous uterine hypertrophy produced. Two similar cases have recently been reported by Bloomfield (1957).

CASE REPORT

History

The patient was aged 57 years, had been married at the age of 40 years and had never been pregnant. She was admitted on 19th November, 1957, from the Accident Room Service of the hospital with a history of lower abdominal pain and vaginal bleeding. The pain, a "dragging" in both iliac fossae, had begun a week previously and was associated with very slight vaginal bleeding. She did not pay much attention to these symptoms at first but, on the day of admission, while out shopping she quite suddenly developed severe lower abdominal cramp-like pain associated with heavy vaginal bleeding in the form of large clots. She quickly returned home and summoned her doctor, who referred her to hospital.

In 1941 she had a left simple mastectomy for a benign tumour and since then had remained trouble-free in that region.

In 1950, when 50 years of age, she consulted her doctor, as she was having regular mild losses for 2 days every month and thought that her periods should have ceased. Her doctor commenced treating her with Stilboestrol tablets, 1 mg. twice daily, which she took regularly, returning each month for a fresh prescription. Shortly after starting to take the tablets her periods ceased completely. From time to time she stopped taking them for a few days but, as vaginal bleeding always began, she commenced taking them again; this promptly stopped the loss. For the previous year she had occasional post-coital bleeding but this was very slight in amount.

She had thus been taking Stilboestrol, mg. 2 daily, more or less continuously for 7 years.

On examination. The patient was a well built healthy looking woman complaining of lower abdominal pain. The pulse rate was 70 and the blood pressure 135/70. There was generalized lower abdominal tenderness with voluntary guarding making palpation difficult. There was slight bleeding. The uterus was soft and enlarged regularly to the size of a 16-weeks pregnancy. The cervix was soft, with a patulous os that admitted a finger quite easily. Vaginal examination produced a temporary exacerbation of her pain and heavier bleeding.

Blood count: Haemoglobin 10·4 g. per cent; packed cell volume 32 per cent, white cell count 15,500 per c.mm.

Provisional diagnosis. Degenerating uterine fibroids with intra-uterine polyp and probable malignant disease of the uterus.

Progress. During the next 24 hours she had a persistent vaginal loss of dark red blood with occasional spasms of pain which were relieved by pethidine. To improve her general condition she was transfused with 2 pints of blood.

Operation, 21st November

A uterine sound would only pass through the cervix in a posterior direction for a distance of 3½ inches and the impression was that the anterior wall of the uterus was replaced by a large soft fibroid. Gentle exploration of the uterine cavity produced large pieces of necrotic, friable, haemorrhagic material whose appearance suggested malignant tissue.

The cervix was closed with a catgut suture, the vagina packed with gauze and laparotomy performed. It was like operating on a pregnant woman with extreme vascularity of all the tissues. The uterus was the size of a 16-weeks pregnancy, globular in shape, very soft and with enormously dilated uterine vessels. The ovaries were both very small and atrophic.

Total hysterectomy and bilateral salpingo-oöphorectomy with removal of a cuff of the vagina was performed. It proved difficult to obtain haemostasis in the vaginal vault owing to excessive vascularity and softness of the tissues. The wound was closed without drainage. A further 1 pint of blood was transfused during operation and the patient's general condition at the close was satisfactory.

Her post-operative recovery was uneventful and she was discharged from hospital on the 12th post-operative day. Her glucose tolerance curve was normal.

Pathological Findings

The uterus opened by a median section down the posterior wall is illustrated in Figure 1 and measures 16 cm. from fundus to external os.

The cavity of the uterus is expanded by a mass of haemorrhagic, cystic, necrotic material confined to the endometrial area with no apparent involvement of the cervical mucosa. The uterine wall is 2·5 cm. thick posteriorly at the point of opening but only 1 cm. at the fundus. The tubes and ovaries are atrophic but otherwise appear normal.

Histological examination reveals much haemorrhage within the uterine mucosa which shows a marked cystic endometrial hyperplasia with typical "Swiss cheese" appearances. There is no suggestion of carcinoma in any of the sections examined and there is no penetration of the muscle layer (Fig. 2).

In the ovaries are a few peritoneal inclusion cysts but they are otherwise atrophic.

Discussion

I think there can be no doubt that in this case the artificial stimulation by Stilboestrol was the cause of the enormous hyperplasia of both endometrium and myometrium. It is not so much the dose of oestrogens which matters but the constant stimulus. While absorption continued there was no lowering of the level of blood oestrogens capable of causing the onset of menstruation. Hence the patient only bled when she discontinued her tablets for a few days.

Many workers believe that oestrogenic substances may play an important role in the aetiology of uterine cancer and Gusberg (1947) reported 5 cases who developed endometrial carcinoma following prolonged oestrogen stimulation. He points out that in those cases developing carcinoma there is probably a genetic factor involved which is required, as well as the stimulus, to produce a malignant change. Novak and Yui (1936) stressed that post-menopausal hyperplasia may be a precancerous lesion and that in such cases the "uterus is better out".

Summary

A case of massive cystic endometrial hyperplasia associated with Stilboestrol administration for 7 years is described. The dangers of prolonged oestrogen stimulation in post-menopausal women are briefly discussed.

Acknowledgments

I am indebted to Mr. Linton Snaith for permission to publish the report of this case and to Dr. B. E. Tomlinson for the pathological details. The photographs were taken by the Department of Photography, King's College, Newcastle upon Tyne.

This case was originally reported at a meeting of the Newcastle upon Tyne Obstetrical and Gynaecological Society held on 6th December, 1957.

References

Bloomfield, A. (1957): *J. Obstet. Gynaec. Brit. Emp.*, **64**, 413.

Gusberg, S. B. (1947): *Amer. J. Obstet. Gynec.*, **54**, 905.

Novak, E., and Yui, E. (1936): *Amer. J. Obstet. Gynec.*, **32**, 674.

FIG. 1

Operation specimen showing the marked hypertrophy of myometrium and endometrium.

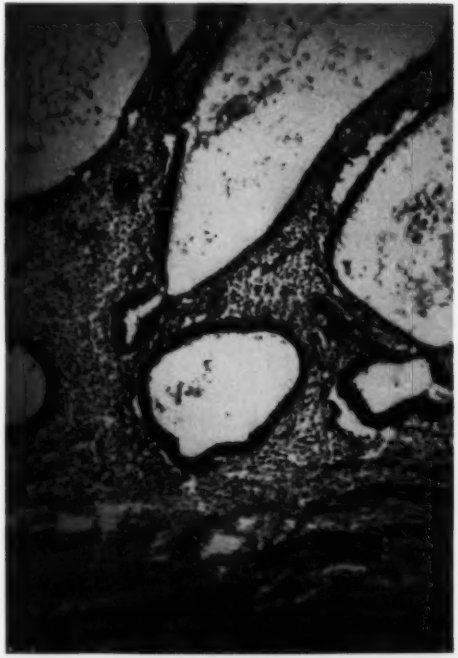


FIG. 2

Endometrium showing typical "Swiss cheese" pattern stopping short at muscle boundary. H. & E. ×80.

SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

BY

K. W. BROWNE, M.A., M.B., D.Obst.R.C.O.G.

AND

DAVID BURMAN, M.B., B.Sc., M.R.C.P., D.C.H.

Kingsbury Maternity Hospital, Charing Cross Hospital Group, London, N.W.9

IN 1907, Fabyan described a newborn infant with multiple areas of induration of the subcutaneous tissue. On the 14th day, the infant was accidentally suffocated and histology of these lesions showed typical fat necrosis. Since then many cases of subcutaneous fat necrosis of the newborn have been described and Masi and Brancolini (1956) were able to find 179 cases in the literature and added 8 new cases. It is a condition, however, which receives only scant attention in the standard textbooks of paediatrics and, even when discussed, the diffuse variety is frequently confused with sclerema neonatorum. Recently, McDonald (1955) has clearly distinguished these two conditions and the salient features of each are summarized in Table I which is slightly modified from the table in his paper.

We describe here two further cases of subcutaneous fat necrosis proven by biopsy and differing from each other in the extent of the lesion. The first is an example of diffuse subcutaneous fat necrosis and in the second there were two localized patches of subcutaneous fat necrosis on the upper arms associated with bilateral radial nerve palsy. This second case is similar to two cases described by Lightwood (1951) and to six cases described by Feldman (1957), but in only one of the latter's cases has a bilateral radial nerve palsy been associated with

TABLE I

Summarizing the Important Features of Sclerema Neonatorum and Subcutaneous Fat Necrosis (Modified from McDonald, 1955)

	Sclerema Neonatorum	Subcutaneous Fat Necrosis
Gestation	About 50 per cent premature	Full-term.
Labour	Usually normal	Usually long or difficult and in primipara.
State at birth	Mostly weak or cyanosed	Mostly needed resuscitation.
Date of onset	Average 9th day	Average 7th day.
State at onset	Weak or debilitated	Healthy babies but may have pyrexia and leucocytosis.
Sites	Whole body except palms, soles and genitalia	Diffuse type—buttocks, shoulders, back and outer aspects of arms and thighs. Local type—cheeks, neck and outer aspects of arm.
Attachment	Skin and deep structures	Skin only—usually movable over deep structures.
Histology	Thickening of subcutaneous connective tissue or nil abnormal	Fat necrosis with foreign-body giant cells, macrophages and fatty acid crystals.
Treatment	ACTH or cortisone	None required.
Prognosis	Without treatment mostly died but now most recover	Baby survives but may develop fat atrophy or subcutaneous calcification.
Cause	? stress disease	? trauma or asphyxia.

bilateral subcutaneous fat necrosis overlying the musculospiral groove. The localized type of subcutaneous fat necrosis has received less attention than the more dramatic, diffuse variety. It is probably commoner than is usually thought and it is possible that Tizard's (1957) case of a brachial plexus palsy associated with soft tissue atrophy in the scapular region is really one of fat necrosis. During the past year, we have seen three cases of nodules in the neck or on the cheeks following a forceps delivery and one case where a subcutaneous induration was felt over the lateral aspect of the forearm following a normal labour and delivery. It is believed that these are localized areas of fat necrosis. These cases are not discussed in detail for we have not proved the diagnosis by biopsy. We agree with McDonald (1955) that this is essential. In all four cases, these lesions have disappeared within 2 months of delivery.

Case Histories

Case 1

A female infant, weighing 8 pounds 12 ounces (4 kg.) was born on 25th February, 1957, after a pregnancy lasting 41 weeks. Her mother had had 2 previous full-term deliveries and was 39 years old. At the 32nd week of pregnancy the uterus was larger than expected and an X-ray showed a single foetus presenting by the vertex with the back to the right. There was a large calcified fibroid in the right wall of the uterus adjacent to the back of the foetus (Fig. 1). Labour lasted 5½ hours and the infant was delivered face to pubes without evidence of foetal distress or neonatal asphyxia.

Two days after delivery the infant had a pyrexia with a rectal temperature between 100° and 101° F. On the 3rd day, the skin over her back was noticed to be reddish blue in colour and beneath this was an area of induration. This indurated plaque was attached to skin but not to deep structures. During the next 6 days the area of induration gradually spread until it covered the whole of the back and buttocks, the outer side of the thighs and the outer side of the upper arms (Fig. 2). These lesions appeared slightly tender. On the 11th day a blood count showed: haemoglobin 121 per cent (17·9 g. per 100 ml.); leucocyte count 11,900 per c.mm. of which 60 per cent were neutrophils, 37 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. The child was discharged on the 13th day having regained her birth weight despite the continuing fever which was unaffected by 3 day courses of oxytetracycline, penicillin and streptomycin.

At the age of 15 weeks she was still fully breast fed and weighed 13 pounds (5·94 kg.). She had developed strawberry naevi over the right thigh, lower lip and right thumb. Apart from these naevi, the skin all over the body was normal. The areas of subcutaneous induration, however, persisted unchanged although the indur..tion over the back was now nodular, the nodules varying in size up to ½ cm. in diameter. At the age of 21 weeks, the subcutaneous tissue over the back showed minimal induration while the lesions over the arms and thighs were nodular. An X-ray showed no subcutaneous calcification. The child now weighed 15 pounds 8 ounces (7·09 kg.), was still fully breast fed and had never had vitamin supplements.

When 9 months old the infant was quite fit and weighed 17 pounds 8 ounces (8 kg.). The skin over the back appeared normal but it was slightly tethered to the subcutaneous tissue and there was a notable absence of subcutaneous fat compared with other sites in the body. Over the outer aspects of the thighs there was irregular atrophy of the subcutaneous fat.

A biopsy was taken on the 8th day from the lesion on the posterior aspect of the right shoulder. Microscopical examination (S.S.332/1957) revealed areas of fat necrosis and slight focal acute inflammation in the subcutaneous fat.

Case 2

A male infant, with a birth weight of 9 pounds (4·11 kg.), was born on 28th April, 1957. His mother was a primigravida aged 25 years whose pregnancy was uneventful. Labour commenced at full-term and the first stage was complicated by primary uterine inertia and lasted 120 hours. It was terminated by an intravenous drip of pitocin, 5 units to 500 ml. of 5 per cent glucose to which 250 mg. of pethidine and 25 mg. of chlorpromazine had been added. The second stage was terminated by a low forceps delivery under local anaesthesia. There was no evidence of foetal distress or neonatal asphyxia.

At delivery the skin over the lateral aspects of the middle part of both upper arms was noticed to be reddish blue in colour and was depressed below the level of the surrounding skin. Beneath the discoloured skin, there was a sharply demarcated area of subcutaneous induration which was attached to skin but not to deep structures. The lesion on the left arm (Fig. 3) was 1 inch (2·5 cm.) by ¼ inch (1·25 cm.) while that on the right was ¼ inch (1·25 cm.) in both diameters. Below the lesion on the right arm was an elongated mass in the subcutaneous tissue ½ inch (1·25 cm.) by ¼ inch (30 mm.) which had the same consistency as the other masses but which was neither attached to skin nor to deep structures.

On the morning after delivery, it was noticed that the child had bilateral wrist drop. Detailed examination showed that there was weakness of the extensors of the right wrist and complete paralysis of the extensors of the left wrist and the left brachia-radialis (Fig. 4). The left triceps was also weak. An X-ray of both arms was normal. The paresis of the right wrist rapidly improved and was normal at 3 weeks. By 6 weeks the muscular power of the left arm was normal.

FIG. 1

X-ray of the abdomen of the mother of Case 1 at the 32nd week of pregnancy showing a large calcified fibroid adjacent to the back of the foetus.

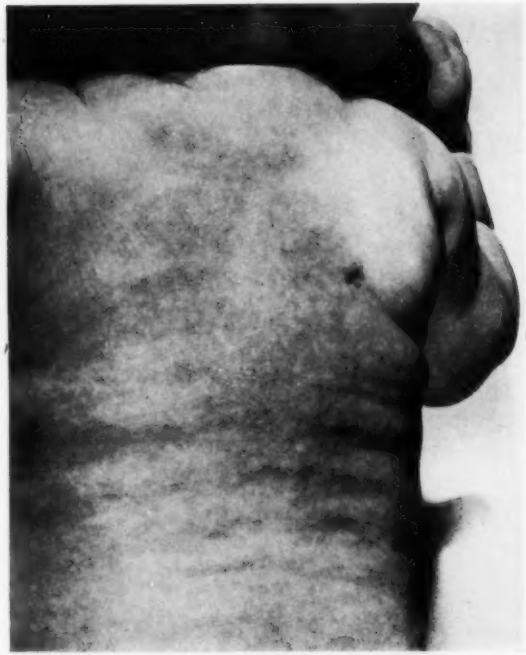


FIG. 2

Photograph to show the area of subcutaneous fat necrosis over the back of Case 1.

FIG. 3

Photograph of the left arm of Case 2 to show the area of subcutaneous fat necrosis. The dark spot above the main lesion is a pigmented mole.

FIG. 4

Photograph to show the left wrist drop in Case 2.

After birth the skin lesions gradually faded until at 6 weeks the skin was normal. The subcutaneous tissue at this time was still indurated but by 16 weeks the induration had disappeared. The skin, however, was still attached to the subcutaneous tissue and depressed below the surface. At the age of 6 months the arms appeared normal but palpation revealed atrophy of the subcutaneous fat with tethering of the skin to the underlying structures.

A biopsy was taken on the 16th day from the edge of the lesion on the left arm. Microscopical examination (S.S. 698/1957) showed areas of fat necrosis and active chronic inflammation in the subcutaneous fat.

Discussion

The lesions of subcutaneous fat necrosis of the newborn are quite characteristic. They usually occur in full-term infants after a long labour or a difficult delivery. The skin overlying the lesions is often bluish red in colour and may be raised above the normal skin surface. The areas of fat necrosis are felt as sharply demarcated areas of induration in the subcutaneous tissue which vary in size from a large pea to areas covering most of the back and buttocks (McDonald, 1955). They are not usually attached to deep structures but are frequently attached to skin which may be impossible to pinch up into folds and which may show the "*peau d'orange*" effect. The common sites for these lesions are the back, cheeks, arms, thighs and buttocks although all areas may be affected except the palms of the hands, soles of the feet, abdomen, axillae and inner aspects of thighs (Fox, 1933). In the diffuse variety there may be a low grade pyrexia and a polymorph leucocytosis but this does not interfere with normal growth (Case 1). Sometimes the lesions soften and liquefy and, if this happens in the presence of a polymorph leucocytosis and fever, the "abscess" may be aspirated or incised. Wright (1954), however, emphasizes that under no circumstances should these lesions be incised and aspiration, also, is probably best avoided.

The importance of recognizing this disease is that, unlike sclerema neonatorum, it carries an excellent prognosis without treatment. Usually the lesions either fade away in a few months or they become more irregular and lumpy, sometimes frankly cystic, and then gradually disappear. In cases reported by Cruse (1876), Pollitzer (1921), Fox (1933), Holzel (1951) and Masi and Brancolini (1956) atrophy of the subcutaneous tissue has been observed and it occurred in both our cases. The prognosis for the radial nerve palsy associated with the localized form of subcutaneous fat necrosis would also appear to be excellent, for in Case 2 the right arm had completely recovered in 3 weeks and the left in 6 weeks. In both Lightwood's (1951) cases and all of Feldman's (1957) cases complete recovery occurred within 3 months but in these cases a splint was applied to the affected limb whereas the only treatment we advised was that the wrists and fingers should be passively moved through a full range of movement at each feed.

In the diffuse type of subcutaneous fat necrosis, calcification has been noted radiologically (Harrison and McNee, 1926; Bernheim-Karrer, 1933) and Clay (1956) and Martin and Steven (1957) have reported cases which developed subcutaneous calcification and a high serum calcium together with the symptoms of idiopathic hyper-calcaemia. Subcutaneous calcification was excluded in Case 1 by an X-ray taken at 21 weeks of age. We did not estimate the serum calcium but at no time has this infant developed symptoms suggestive of hypercalcaemia. This infant was entirely breast-fed for the first 5 months and was given no vitamin supplements whereas the cases of Clay (1956) and Martin and Steven (1957) were both artificially fed and both received vitamin supplements. In view of this evidence, it would probably be wise to give very little vitamin D to patients who develop subcutaneous fat necrosis and this can best be arranged by continuing breast feeding as long as possible or ensuring that the patient is given the new stocks of National dried milk which contain only 100 I.U. of vitamin D to the dry ounce (28 g.) (*Lancet*, 1957).

The aetiology of subcutaneous fat necrosis of the newborn is usually considered to be either birth injury (Bojlen and Petri, 1936) or asphyxia (Holzel, 1951) or a combination of both. In our cases we believe that trauma *in utero* is the cause. In Case 1 labour was normal and the delivery was easy although the baby was born face to pubes. Fat necrosis first appeared over the infant's back, which is seen

in Figure 1 to lie close to the calcified fibroid. This position was maintained during labour and we suggest that the uterine contractions caused the fibroid to compress the back of the foetus and produce subcutaneous fat necrosis.

In Case 2 the fat necrosis was present at birth and the centre of the lesions was depressed below the surrounding skin. This could be explained if the lesion had been present for a time sufficient to allow atrophy or fibrosis of the subcutaneous tissue to occur, although a biopsy taken through the edge of the lesion showed neither of these features. As the areas of fat necrosis were not attached to deep structures, and as the severity of the paralysis was maximal at onset and improvement occurred so rapidly, it is likely that the radial nerve palsy and fat necrosis were due to the same pressure rather than involvement of the nerve in the inflammatory process. The latter was observed, however, in a case described by Zeek and Madden (1946). The mother of Case 2 was a primigravida who had a long labour complicated by uterine inertia and these were the conditions which Feldman (1957) found favoured the development of subcutaneous fat necrosis of the arm associated with a radial nerve palsy. Feldman suggested that the cause of these lesions was a uterine constriction ring which may not be diagnosed clinically, but he admitted that uterine action appeared normal in two of his cases. This explanation is difficult to accept because a constriction ring alone would compress both arms and also the tissues overlying the vertebrae whereas fat necrosis and radial nerve palsy is usually unilateral and it has not yet been associated with localized fat necrosis over the thoracic spine. We believe that the infant produces the lesions himself by compression of his upper arm with the opposite hand when he lies *in utero* with his arms folded. The lesion will then be unilateral in the majority of cases since it will be uncommon for both hands to lie over the opposite musculo-spiral grooves. The pressure exerted upon the hand would depend upon the tone of the uterine muscle and the strength and duration of contractions. Prolonged labour with hypertonic uterine inertia or constriction rings in a primigravida will therefore be the factors most likely to produce this abnormality.

Summary

Two cases of subcutaneous fat necrosis in the newborn are described. The first is an example of the diffuse variety and is thought to be due to a calcified fibroid compressing the back of the foetus during labour. In the second, there were two localized patches of subcutaneous fat necrosis on the arms associated with bilateral radial nerve palsy. It is suggested that the palsy is due to compression of the radial nerve in the musculo-spiral groove by the infant's opposite hand and that the pressure on the hand will be increased by abnormal uterine action.

The characteristics of this disease, its prognosis and its differentiation from sclerema neonatorum are discussed, together with the role of vitamin D in subcutaneous calcification and hypercalcaemia.

Acknowledgments

We are grateful to Dr. C. T. Potter for permission to publish these cases and for helpful advice and criticism. We also wish to thank Dr. J. C. Sloper for his histology reports and Dr. W. S. Phillips for permission to publish the X-ray. The figures were kindly prepared by Miss P. M. Turnbull of the Photographic Department.

References

Bernheim-Karrer, J. (1933): *Z. Kinderheilk.*, **55**, 695.

Bojlen, K., and Petri, S. (1936): *Acta paediat., Uppsala*, **19**, 123.

Clay, P. R. (1956): *Proc. R. Soc. Med.*, **49**, 598.

Cruse, P. (1876): *St. Petersb. med. Wschr.*, **1**, No. 20, 3.

Fabyan, M. (1907): *Bull. Johns Hopk. Hosp.*, **18**, 349.

Feldman, G. V. (1957): *Arch. Dis. Childh.*, **32**, 469.

Fox, H. (1933): *Arch. Derm. Syph.*, **27**, 237.

Harrison, G. A., and McNee, J. W. (1926): *Arch. Dis. Childh.*, **1**, 63.

Holzel, A. (1951): *Arch. Dis. Childh.*, **26**, 89.

Lancet (1957): *Lancet*, **2**, 737.

Lightwood, R. (1951): *Arch. Dis. Childh.*, **26**, 436.

McDonald, R. (1955): *S. Afr. med. J.*, **29**, 1007.

Martin, M. M., and Steven, E. M. (1957): *Arch. Dis. Childh.*, **32**, 146.

Masi, A., and Brancolini, L. (1956): *Riv. clin. Pediat.*, **57**, 362.

Pollitzer, R. (1921): *Riv. clin. Pediat.*, **19**, 435.

Tizard, J. P. M. (1957): *Proc. R. Soc. Med.*, **50**, 330.

Wright, C. S. (1954): *in* Nelson, W. E. (ed.): *Textbook of Pediatrics*. 6th edition. Saunders, Philadelphia. p. 1367.

Zeek, P., and Madden, E. M. (1946): *Arch. Path.*, **41**, 166.

ACROPARAESTHESIA IN PREGNANCY AND THE CARPAL TUNNEL SYNDROME

BY

KEITH B. LAYTON, M.B., M.R.C.O.G.
Honorary Associate Surgeon
Royal Women's Hospital, Melbourne

NUMBNESS, tingling and pain in the hands and fingers during pregnancy is usually mild but on occasions may be a severe disability. The term acroparaesthesia has commonly been used to describe the abnormal sensations. These symptoms are often a manifestation of the carpal tunnel syndrome which shows a definite tendency to be associated with pregnancy.

The carpal tunnel syndrome is caused by compression of the median nerve in the carpal tunnel, and is characterized by acroparaesthesia in the hand and fingers in the area supplied by the median nerve, with associated objective manifestations in some cases. The symptoms are commonly nocturnal.

Reid (1956) reviewed the literature, and reported 28 cases, and Garland, Bradshaw and Clark (1957) described the clinical features in 53 cases. These and previous writers have pointed out the association of this condition with pregnancy, the menopause, and acromegaly. Wallace and Cook (1957) reported 2 cases associated with pregnancy, one of which was treated surgically.

The purpose of this paper is to describe 7 cases of the carpal tunnel syndrome in pregnancy, and the use of oestrogen therapy in its conservative management.

AETIOLOGY

The median nerve passes through the carpal tunnel beneath the flexor retinaculum in company with the common flexor group of tendons. Any local intrusion such as arthritis of the wrist, or any thickening of the ligamentous boundaries or contents of the carpal tunnel, may be responsible for compressing the median nerve. In many cases, however, no such aetiological factor is found. At the operation of division of the flexor retinaculum for the relief of intractable symptoms, a tight carpal tunnel with median nerve compression, and a proximal "neuroma", with oedema of the nerve in some cases, has been repeatedly demonstrated.

An adequate explanation, however, of the association of this syndrome with such diverse conditions as pregnancy, the menopause and acromegaly, has not been supplied. Endocrine factors have been postulated by many writers, and, as pointed out by Kremer *et al.* (1953), whatever the endocrine disturbance may be, its effect in this syndrome appears to depend on an increase in the volume of the carpal tunnel. Water retention in the tissues with resultant nerve compression is an obvious possibility in pregnancy, and will explain the spontaneous recovery following delivery.

The exacerbation of symptoms at night may be due to extra warmth increasing the oedema and hence the pressure on the nerve, but Reid (1956) suggests it is due to increased relative ischaemia in the nerve caused by increased metabolism when the limb is warm. He points out the similarity to the pain at night and the relief when the limb is dependent which occurs in cases of ischaemia of the lower limbs due to vascular occlusion.

Clinical Features

The condition usually presents as nocturnal attacks of acroparaesthesia in one or both hands, and in the thumb and lateral three fingers. Some patients initially state that all fingers are involved, and it is not until close questioning, or more careful observation of symptoms by the patient, that it is found that the little finger is unaffected. Occasionally pain is also referred along the middle of the forearm to the elbow. In addition to acroparaesthesia, symptoms of swelling and stiffness of the hand and fingers, and associated clumsiness may be reported. In mild cases symptoms are often only noticed on awakening, but in severe cases little sleep can be obtained. Temporary relief is often found by hanging the arm over the side of the bed, and in nearly all cases improvement occurs with the use of hands during the day. Objective neurological signs are uncommon in pregnancy, but there may be anaesthesia over the median nerve distribution in the hand and fingers, and signs of thenar muscle wasting.

Diagnosis

The characteristic features should make the diagnosis obvious. A confirmatory test is described by Gilliatt and Wilson (1953). A sphygmomanometer cuff is placed above the elbow and inflated to above systolic arterial pressure and this exacerbates the paraesthesia in the median nerve territory in less than one minute. In the normal subject symptoms do not occur so quickly, and are felt over the entire hand, and usually first felt in the ulnar nerve distribution. This test, however, has not been found of great diagnostic value in this series of cases.

The carpal tunnel syndrome must be differentiated from:

(1) Spondylosis and cervical disc lesion—a nerve root is involved in this condition and the distribution is not that of the median nerve.

(2) Thoracic outlet syndrome—this is usually a combination of vascular and neurological phenomena involving the first thoracic nerve.

(3) Peripheral neuritis—the areas affected are usually of the "glove" distribution.

All of the above conditions are far less common in pregnancy than the carpal tunnel syndrome. In cases of doubt the response to the simple therapeutic administration of oestrogens may be helpful.

Case Reports

Case 1

Mrs. M., a multigravida, aged 28 years, when 14-weeks pregnant first noticed numbness, tingling and pain in the right hand over the distribution of the median nerve. Symptoms occurred at night, and were relieved by hanging the arm over the side of the bed and exercising the hand. The symptoms became steadily worse, and, by the 24th week of pregnancy were present during the day as well, and were associated with stiffness of the wrist and fingers. There was minor weakness of the thenar muscles, but no obvious wasting. Vitamins, simple analgesics and sedatives gave no worthwhile relief.

A diagnosis of carpal tunnel syndrome was made by Reid (1956) and oestrogen therapy was advised. This was commenced with 5 mg. Stilboestrol 3 times daily, and the dosage doubled each day until 150 mg. daily was taken. Improvement was noted within one week, and after 3 weeks the symptoms were greatly relieved. After 8-weeks treatment (now 32-weeks pregnant) the only complaint was some numbness over the thumb, and at the 36th week of pregnancy she reported only occasional tingling in the hand. The dose of Stilboestrol was progressively reduced until term when a normal delivery occurred. Stilboestrol was not given after delivery as symptoms were not troublesome, and by the 6th week of the puerperium the hands were normal and there has been no further trouble.

Case 2

Mrs. Y., primigravida, aged 38 years. The antenatal period was normal until 20 weeks when she developed nocturnal paraesthesia and pain in both hands and fingers over the median nerve distribution. The symptoms woke her at night and were relieved by hanging the arms over the side of the bed and by use during the day. At the 22nd week of pregnancy the symptoms were much more severe, and there was also pain down the forearms. Stilboestrol therapy was instituted in the same dosage as Case 1. For two weeks there was little change, and then rapid improvement occurred so that by the 26th week of pregnancy there was no pain and only slight numbness. Stilboestrol was then discontinued to observe if the pain recurred.

When seen again at the 30th week the symptoms were as severe as previously and Stilboestrol was recommenced and when seen two weeks later there was marked relief of symptoms. Treatment was again interrupted with exacerbation of symptoms, and subsequent relief on

recommencing Stilboestrol, which was then continued to term. Oedema and mild hypertension necessitated a surgical induction of labour at term, and spontaneous delivery of a healthy male child resulted. Symptoms improved slowly after delivery and had completely subsided 6 weeks later. Oestrogens were not given in the puerperium as the patient was breast feeding.

Case 3

Mrs. D., primigravida, aged 35 years, was well until 25-weeks pregnant when she complained of "neuritis" in the hands. Ethinyl Oestradiol 0·05 mg. twice daily was given.

At 30 weeks the pain had now become very severe in the right hand, and was present but less severe in the left hand. On closer questioning it was noted that the pain occurred only at night, and was over the distribution of the median nerve in the hand and fingers. A diagnosis of carpal tunnel syndrome was made, and Stilboestrol was given in increasing dosage until 150 mg. daily was being taken by the fifth day of treatment, and treatment was continued until delivery. Within a few days the pain had eased considerably and steady improvement continued until only slight numbness persisted. At 37 weeks this patient developed pre-eclamptic toxaemia with oedema and albuminuria. A Caesarean section was performed on account of associated features of a breech presentation in an elderly primigravida.

Two weeks after delivery symptoms recurred in the right hand. Ethinyl Oestradiol 0·05 mg. three times daily was given (the patient was not breast feeding) and 2 weeks later there was mild improvement, but not the dramatic relief which occurred in pregnancy. Three months after delivery there was still occasional pain and numbness in the hands. Oestrogens were discontinued as the disability, unlike in pregnancy, was not now severe. Further follow-up of this case will be necessary.

Four other cases have been seen in pregnancy, but these were relatively mild and did not require oestrogens. All spontaneously improved after delivery.

Discussion

The use of oestrogens in the treatment of carpal tunnel syndrome in pregnancy is empirical as its cause in pregnancy is not understood. Oedema is unlikely to be the sole aetiological factor when Cases 2 and 3 are considered. Here the symptoms were maximal before oedema was present, and when oedema did occur the condition was relieved by oestrogens. Also many patients with generalized pregnancy-oedema have been questioned about their hands, and none apart from the cases described had symptoms. Relief of this syndrome in pregnancy with oestrogens is curious in view of the existing high oestrogen concentration. It is paradoxical that menopausal patients with low oestrogen levels are also prone to this condition, and are similarly relieved by oestrogens.

Conservative treatment is advisable in pregnancy as spontaneous recovery is usual after delivery, although it is not always immediate, as in Case 2. Surgical division of the retinaculum should be reserved for cases with intractable symptoms, or cases where the condition has progressed to a degree that thenar muscle wasting is evident.

Summary

(1) The carpal tunnel syndrome as a cause of acroparaesthesia in pregnancy is discussed.

(2) The aetiology, clinical features and management are considered.

(3) Seven cases are reported, 3 in detail.

(4) Oestrogens have proved of value in the conservative management of this condition.

Acknowledgments

I would like to thank Mr. S. F. Reid for first bringing this condition to my notice and for his encouragement in preparing this paper. I am indebted to Dr. W. J. Rawlings and Dr. G. D. Ley for permission to publish the details of Case 2, which was seen in their clinic at the Royal Women's Hospital, Melbourne.

References

Garland, H., Bradshaw, J. P. P., and Clark, J. M. P. (1957): *Brit. med. J.*, **1**, 730.

Gilliatt, R. W., and Wilson, T. G. (1953): *Lancet*, **2**, 595.

Kremer, M., Gilliatt, R. W., Golding, J. S. R., and Wilson, T. G. (1953): *Lancet*, **2**, 590.

Reid, S. F. (1956): *Aust. N.Z. J. Surg.*, **25**, 204.

Wallace, J. T., and Cook, A. W. (1957): *Amer. J. Obstet. Gynec.*, **73**, 1333.

STANDARDS IN OBSTETRICS

A Plea for Uniform Standards in Maternity Statistics and Hospital Reports

BY

F. J. BROWNE, D.Sc., M.D., F.R.C.S., F.R.C.O.G.

Emeritus Professor of Obstetrics and Gynaecology, University of London

Consulting Obstetric Surgeon, University College Hospital, London

THE Royal College of Obstetricians and Gynaecologists, London, did good service to obstetrics by the issue in 1948 of a recommended Standard Form of Annual Maternity Hospital Reports (*Journal of Obstetrics and Gynaecology of the British Empire*, 1948). This form has been widely used in Great Britain and the Commonwealth but was in some respects unsatisfactory. One important fault was the inclusion of all varieties of toxaemia of pregnancy in one single table without any differentiation between them. The College has now (*Journal of Obstetrics and Gynaecology of the British Empire*, October, 1957) issued a revised Standard Form which replaces that of 1948. This is an improvement on the old Form but is, in my opinion, still defective in many respects. It is, too, rather horrifying that the College recommends that to reduce cost, though the Standard Annual Report should be "produced" in every maternity hospital and department and retained, only a Summary need be printed for general distribution. Does this mean that every one who wishes to consult the full Report of a Hospital in, say, Birmingham or Liverpool must journey to Birmingham or Liverpool to do so? It should be noted that it is recommended that the Report be "produced", and not necessarily printed. It will probably be kept in type so as to be available for reference by those who are able to make the journey. No better way of suppressing criticism of hospital reports, or of rendering non-available the information contained in them could be imagined.

It has been obvious for many years that, unless uniform standards and definitions are adopted, comparison of results in different hospitals and countries is impossible. In this respect the new standard report does little to help. In the introductory remarks, for example, it is stated: "it was thought impracticable . . . to define pre-eclamptic toxaemia." If impracticable why include three tables with the headings, pre-eclampsia, chronic hypertension, and chronic nephritis? Without a definition how is the compiler of the report to know what is to be included in each table? No doubt each will have a standard of his own, and a standard implies a definition. Apparently the compiler, usually a Registrar, is expected to furnish a definition though the College is unable to do so.

If each hospital has its own definition, though its Report states what it is, results can seldom be compared. In addition to drawing attention to deficiencies in the new Standard Report it is the purpose of this paper to suggest some standards and definitions in the hope that they may receive general acceptance.

TOXAEMIAS OF PREGNANCY

Pre-eclamptic Toxaemia

I suggest that pre-eclamptic toxaemia be defined as "a rise of blood pressure above 120/80, occurring for the first time after the end of the 20th week counted from the first day of the last menstrual period (the diastolic pressure being noted at the point of disappearance of

the sound) irrespective of whether or not there is oedema, abnormal weight-gain, or albuminuria, and no matter what the patient's age is". For the blood pressure to be considered raised either the systolic or diastolic pressures or both must be raised above this level and neither must be below it. Thus neither 138/70 nor 110/85 would be hypertensive though the systolic and diastolic pressures are raised in the first and second respectively.

In many clinics it is customary, if the blood pressure is raised at the first taking, to rest the patient for a time and take it again, recording that as the true level if it is lower. I believe that this is wrong and the true reading is the first.

The 120/80 standard has been criticized as being too severe (some have called it "ridiculous"). It is however becoming more generally accepted and is now used at the Post Graduate Medical School of London, by Lennon of Bristol, by Bruce Mayes of Sydney, and by Vartan of London. In a discussion on the prevention of eclampsia at the Royal Society of Medicine, London, Vartan (1957) said "I believe that the high incidence of eclampsia is very largely due to the regarding of figures well above 130/70 as being within the normal range . . . I think I have shown that eclampsia is most prevalent in those hospitals and schools where the information obtained by those who have studied the normal blood pressure has been so lightly set aside."

Here let me explain how the 120/80 standard came to be adopted. In 1933, in a paper entitled "The early signs of pre-eclamptic toxaemia with special reference to the order of their appearance and their interrelations", I stated: "The normal limit of blood pressure has been taken as 130/70 for patients of all ages—the diastolic pressure being recorded when the sound disappears." This standard was used in the obstetric unit, University College Hospital, London, till 1941, when, influenced by the papers of Robinson and Brucer (1939, 1940) it was changed to 120/80 which I have since used and now recommend. The 140/90 standard more commonly used by obstetricians is, in my opinion, dangerously high, and too near the, for the foetus, lethal level of 160 systolic and 100 diastolic. Above 160 systolic retro-placental bleeding is apt to occur (together with albuminuria); at 100 diastolic the foetus is liable to die from anoxia.

Relativity of Blood Pressure. In 1948 Dixon Hughes of Sydney, believing that no case of eclampsia was unpreventable, objected to an arbitrary level of normal blood pressure, whether 120/80 or 140/90, and insisted on a patient's admission to hospital if her diastolic blood pressure was consistently raised by more than 10 millimetres of mercury over her basic blood pressure as determined at her first visit to the antenatal clinic. There is no doubt that such a relative rise might well be regarded as an early warning sign, or even as an early manifestation of pre-eclamptic toxaemia, demanding special precautions. At the same time there are advantages in having a fixed standard above which it can be said "this patient has hypertension" whether it be "chronic hypertension" or the acute form characteristic of pre-eclamptic toxaemia, and for purposes of classification such a fixed standard would indeed seem to be indispensable.

Chronic Hypertension

I suggest that this should be diagnosed if the blood pressure is raised for the first time above the 120/80 level before the end of the 20th week. There is often a familial history of hypertension, and sometimes the patient is known to have had hypertension before pregnancy began—perhaps a relic of pre-eclamptic toxaemia or eclampsia in a previous pregnancy.

Chronic Nephritis

This is rare in pregnancy, probably not more than 1 in 1,000 pregnancies. The diagnosis may be very difficult and it is generally necessary to admit to hospital for observation and tests of renal function. There is often a history of acute nephritis in childhood, and the albuminuria is present before the end of the 20th week and usually without any marked rise in blood pressure.

Unclassifiable Toxaemia

The exact kind of toxaemia cannot usually be classified if the patient is seen for the first time after the end of the 20th week unless she is a

chronic hypertensive and known to be so before pregnancy began.

Maturity

In each table of the Standard Report there is a column headed "Maturity". This means the stage to which pregnancy had advanced at the time the particular abnormality (e.g., abortion, ante-partum haemorrhage) arose. But no direction is given as to how maturity is to be estimated. I suggest that it should be done by counting the number of weeks and days from the first day of the last menstrual period. This, of course, does not give the duration of pregnancy which is usually about 14 days less, but it would provide a sufficiently accurate standard for comparison. Where there is an obvious discrepancy a question mark might be inserted after the estimate given.

Placenta Praevia

It is now widely accepted that this should only be diagnosed when the placenta is seen or felt to encroach on the lower uterine segment. This was stated clearly in the 1948 Standard Report but has been omitted in the present one. As the latter is said to replace the 1948 recommendation the omission is regrettable. Incidentally it should be emphasized that placenta praevia should not be diagnosed, as it often is, from the position of the hole in the membranes after delivery of the placenta.

Nomenclature of Placenta Praevia

In the year 1932 cases of placenta praevia admitted to University College Hospital, London, began to be classed into four degrees according to the amount of encroachment on the lower uterine segment. This replaced in our Annual Reports the old terminology of "Marginal" and "Lateral" which were often confused with each other even in textbooks. The degrees were as follows:

First degree: Placenta dips into the lower uterine segment but stops short of the internal os.

Second degree: Placenta reaches internal os.

Third degree: Placenta overlaps internal os when closed but not when fully dilated.

Fourth degree: Placenta is "central" so that its centre corresponds roughly to the internal os, and therefore still overlaps the os when it is fully dilated.

Though used in our own (University College Hospital) Annual Report it was not, so far as I know, adopted elsewhere. Macafee of Belfast in his well-known paper on placenta praevia in 1945 changed "degree" to "type" and this has since come largely into use and is recommended for use in the Standard Report. In my opinion however "type" is less correct. The dictionary defines "type" as something that represents or symbolizes something else: an image, emblem or symbol; and "degree" as "one of a succession of steps, grades, or stages", which each degree of placenta praevia obviously is. The word "type" of course runs more trippingly off the tongue, but that does not justify its use at the expense of correctness.

A Table for Accidental Haemorrhage is included in the recommendations for the Standard Report and another for "Ante-partum Haemorrhage of Doubtful Origin" but there is none for "Ante-partum Haemorrhage of Extra-placental Origin", such as cervical polyp, cancer of the cervix, etc. A few of these cases occur in every maternity hospital and a table for them should be included in the annual report.

Stillbirth and Live Birth

The definition of a stillborn child given in the Standard Report is "one born at or after the completion of the 28th week of pregnancy and which fails to breathe after birth". This definition is exceedingly defective. Apart from the fact that it is impossible to say when pregnancy begins, and therefore the duration of pregnancy, but only the number of days that have elapsed from the first day of the last menstrual period, there is no special reason for adopting the 28th week as the limit. Why not the 27th or the 24th? Unless a more accurately ascertainable standard is used stillbirth rates of different countries will not be comparable. In the Chicago Lying-in Hospital stillbirths include all foetuses weighing 400 g. or over, and I suggest that 400 g. should be adopted as the standard in the College Report.

For purposes of registration of stillbirths in England and Wales the Registrar General has ruled as follows: For purposes of registration of stillbirths the Births and Deaths Registration Act 1953 (Section 4) defines stillborn child as "a child which has issued forth from its mother after the twenty-eighth week of pregnancy and which did not at any time after being completely expelled from its mother breathe or show any other sign of life" (Wood, 1957). In this definition there is confusion. In the first place a child born by Caesarean section is never "expelled" from its mother. In the second place the definition does not state what is meant by "other sign of life". What other sign? I do, however, like the phrase "issued forth from its mother". Was it not Aristotle who taught that the child crept out of the womb, as it were under its own steam? There is still a lot to be said for this view!

The World Health Assembly in 1950 defined a live birth as "the complete expulsion or extraction from its mother of a product of conception which after such separation breathes or shows any evidence of life such as beating of the heart, pulsation of the umbilical cord or definite movements of the voluntary muscles whether or not the umbilical cord has been cut or the placenta is attached". In my opinion this definition is not satisfactory. An embryo not more than 3 inches long removed from the abdomen at operation for ruptured tubal pregnancy, or a tubal abortion of similar size may show the heart beat plainly. How many gynaecologists have not demonstrated it to nurses? Is this embryo to be classified as a live birth? According to the definition of the World Health Assembly it is!

I suggest that the definition of a "live birth" should be: "A child that breathes after birth whether or not the placenta is attached or the cord cut, and that weighs not less than 400 grams." A "stillbirth" should be defined as "a foetus that fails to breathe after birth, and weighs at least 400 grams". This brings the minimum weight into conformity with that of the Chicago Lying-in Hospital where during the 2 years 1954 and 1955 the stillbirth rate was 1·5 per cent and the perinatal mortality 2·7 per cent. This standard involves the adoption of the metric scale which is of course more accurate, as 1 ounce is only roughly equivalent to 30 grams, and few hospitals weigh to a smaller fraction than ¼ ounce. Besides, weight ratios, sometimes important, are more easily computed on the metric scale.

Premature Live Birth

This is defined in the Standard Report recommendations as "a birth weight of 5½ pounds and under". This leaves it to any particular hospital to fix its own minimum standard of premature live birth, and hospitals vary considerably in their standard of "viability". Statistics of mortality among premature infants are therefore not comparable. Again I suggest that the lower limit should be fixed at 400 grams.* A premature live birth would therefore be "a child that breathes after birth whether or not the placenta is attached or the cord cut, and that weighs not less than 400 grams (14⅛ ounces), nor more than 2,500 grams (5½ pounds).

Neonatal and Perinatal Deaths

Neonatal death is defined both by the National Office of Vital Statistics, U.S.A., and by the Registrar General (England and Wales) as "deaths among live born infants under 4 weeks of age per 1,000 live births". Yet the definition of the Royal College for the Standard Report is as follows: "Deaths within 28 days either in hospital or after transfer to another hospital *but excluding those discharged healthy*." If this is followed, many hospital reports will not return a correct neonatal mortality. All the Report can do is to give a correct "perinatal mortality", by which is meant "stillbirths and early neonatal deaths (deaths under one week) per 1,000 total (live and still) births". But perinatal mortality is not asked for in the Standard Report. Admittedly an accurate return of neonatal deaths occurring after discharge from hospital to the parents' home may be difficult to get unless a follow-up for 28 days can be arranged. But surely this should not be impossible in modern hospitals with

* Premature live born infants should be weighed within 12 hours after birth.

infant welfare clinics attached. Unless it can be done it would be better to omit neonatal mortality altogether and substitute perinatal mortality which can be given accurately, provided of course that, as I have suggested above, a uniform minimum weight standard is used for stillbirths and deaths in the first week. After all, correct neonatal mortality rates are always available for study in the official National Statistical Reviews.

It would be, of course, advisable and indeed necessary to give also the stillbirth and early neonatal death components of the perinatal mortality, otherwise the incidence of neonatal death in the first week would not be apparent.

Congenital Abnormalities

The incidence of these will obviously vary according to what is included, yet the Standard Report gives no directions on this point. Should minor defects be included, such as naevus, hydrocele, accessory nipple, etc., or only those that would seriously handicap the child, or interfere with its development? Should malformed embryos be included? In a very carefully planned investigation at the Sloane Hospital for Women, New York, of 5,739 products of conception weighing 500 g. and over, McIntosh *et al.* (1954) found congenital abnormalities in 7·5 per cent. They included in the survey only women booking for confinement at or before the 4th month of pregnancy so as to exclude patients referred to the hospital because of some abnormality. Such minor abnormalities as those above mentioned were included as well as the most serious. Davis and Potter (1956) on the other hand, from a study of 500 consecutive births at the Chicago Lying-in Hospital, and including only serious abnormalities likely to handicap a surviving child or interfere with its development, found that about 1 per cent of all foetuses who pass 20 weeks of intra-uterine life fall into this category. Most of the British Hospital Reports since 1948 give lists of congenital abnormalities; some however exclude infants that died; others include only infants born alive. Among 14 recent British reports the incidence varied from 0·9 per cent to 3·0 per cent, the average being 1·7 per cent, so it would seem, judging from the incidence of 7·5 per cent in the series of McIntosh and colleagues quoted, that only major abnormalities have been included in any of the reports.

I suggest that some directions should be given in the Standard Form and that only foetuses or infants weighing 400 g. or over should be included. It should be clearly stated too what abnormalities are to be excluded.

Maternal Death

The definition of what constitutes a maternal death has always presented considerable difficulty, so much so that statistics of Maternal Mortality from different states and even from different hospitals in the same state are incomparable. The Standard Report of the Royal College, though it asks for particulars of maternal deaths does not give any definition of maternal death or directions as to what is to be included. The Registrar General's Statistical Review of England and Wales divides Maternal Mortality into (1) "That due to complications of pregnancy, childbirth and puerperium (including abortions), and (2) those deaths not classed to pregnancy or child-bearing but certified as associated therewith" (such causes as pneumonia, heart disease, influenza, pulmonary tuberculosis, diabetes, thyrotoxicosis, etc.). None of these deaths from associated diseases are included in the Maternal Mortality Rates. For example in 1953 the Maternal Mortality in England and Wales due to (1) was 0·75 per 1,000 total births and to (2) 0·18 per 1,000 total births. The total maternal death rate therefore was 0·94. But which is to be quoted as the Maternal Mortality rate for England and Wales? The position is, to say the least, confusing. It might even be regarded as not quite honest. A patient, for example, suffering from mitral stenosis might have survived for many years had she not become pregnant, the congestive failure which caused her death having been precipitated by the added burden of childbearing.

Again, how long after delivery may a death be classed as "maternal"? If a woman with pulmonary tuberculosis dies of it 12 weeks after delivery is it a maternal death? Are we quite sure that her tuberculous condition was not

aggravated by the pregnancy and confinement? Authorities could be quoted both ways.

Reid (1957) draws attention to the inaccuracy of Maternal Mortality figures in the United States where, he says, "some 20 to 30 per cent of maternal deaths are not so classified and are reported as deaths due to non-obstetrical causes . . . In Massachusetts as in many States there is no precise definition in the statutes but it has been arbitrarily accepted (by the Maternal Welfare Committee of the State Medical Society) that the death of a patient from any cause during pregnancy or within 90 days following delivery is, or should be, classified as a maternal death."

As an example of the confusion arising from absence of a precise statutory definition Reid quotes "the recent Michigan study on Maternal Mortality" where fatalities from heart disease were classified as among the non-obstetrical deaths. "For this and other causes", he states, "approximately one-third of the total obstetrical deaths are regarded as non-obstetrical; . . . unless one includes all deaths as defined above, the maternal mortality will become artificial and arbitrary."

I suggest therefore that the following definition of maternal death should be adopted: "The death of a woman occurring from any cause during her pregnancy or confinement or within 6 weeks after delivery."

I suggest too that the Royal College should try to get the Registrar General (England and Wales) to adopt the same standard in his Annual Statistical Review. The only question that might be disputed in this definition is the number of days after delivery that should be included. I believe it should not be less than six weeks and it might well be more—even the 90 days of the Massachusetts definition. More important than the actual number of days is attainment of a uniform standard that will be acceptable in all countries.

Summary

Defects in existing standards and definitions used in maternity statistics are discussed, and alternatives suggested that are believed to be correct.

A plea is made for the adoption of uniform standards so that statistics of different hospitals and countries can be compared.

References

Browne, F. J. (1933): *J. Obstet. Gynaec. Brit. Emp.*, **40**, 1160.

Davis, M. E., and Potter, Edith L. (1956): *Pediatrics*, **19**, 719.

Macafee, C. H. G. (1945): *J. Obstet. Gynaec. Brit. Emp.*, **52**, 313.

McIntosh, R., Merritt, Katherine K., Richards, Mary H., and Bellows, Marjorie J. (1954): *Pediatrics*, **14**, 505.

Reid, D. E. (1957): *Amer. J. Obstet. Gynec.*, **73**, 697.

Robinson, S. C., and Brucer, M. (1939): *Arch. int. Med.*, **64**, 409.

Robinson, S. C., and Brucer, M. (1940): *Arch. int. Med.*, **66**, 393.

Vartan, C. K. (1957): *Proc. R. Soc. Med.*, **50**, 795.

Wood, Audrey (1957): *Brit. med. J.*, **2**, 1306.

THE OBSTETRIC MEDICINE RESEARCH UNIT, ABERDEEN

On 22nd April, 1958, new accommodation to house the Obstetric Medicine Research Unit of the Medical Research Council was opened at Foresterhill, Aberdeen, by Sir John Erskine, Chairman of the Scottish Hospitals Endowments Research Trust. The Trust generously offered £60,000 to Aberdeen University to build new accommodation for the Unit, and the North East Regional Hospital Board gave the site, equipped the beds and provided the necessary nursing and domestic staff. The Medical Research Council provided the research staff and equipment. Since the co-ordination of research with day-to-day clinical practice was regarded as of over-riding importance, the new accommodation was built on top of the antenatal wing of the Aberdeen Maternity Hospital. It includes wards for eight patients, a metabolic kitchen, ancillary clinical accommodation, several laboratories and offices. The construction is sufficiently flexible to permit relatively easy adaptation if future research plans called for modification of the structure.

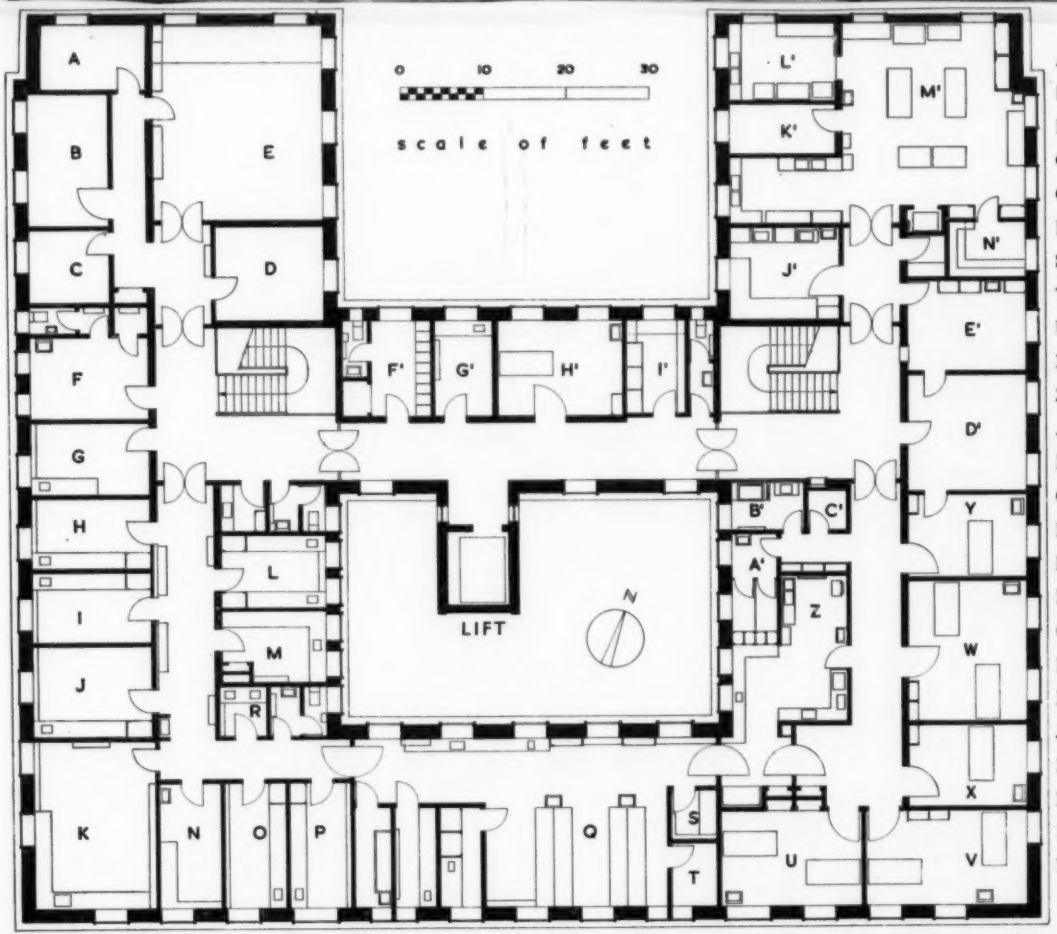
The new floor has a Mansard roof with sufficient head room to contain the service mains, water tanks, etc. Internally, bearing walls have been reduced to a minimum in the interests of possible future modifications. The floor plan is shown in the diagram (Fig. 1). The outline has, of course, been dictated by that of the existing structure.

Some features in the internal arrangements are of special interest. No water-closets have been provided for patients, to facilitate collection of excreta for analysis and to minimize accidental losses. After use, the collection pans of special dry-closets are put into refrigerated lockers—one for each patient—which open from the rear of the closet into an annexe between the main biochemical laboratory and the sluice room. Here measurements can be made and aliquots removed for chemical analysis; samples may be stored in an adjacent deep-freeze cabinet.

The main biochemical laboratory has been designed to minimize hazards and unpleasant smells or noises. Processes likely to cause unpleasant odours are carried out in a special room fitted with an air extraction duct in addition to fume cupboards. A similar room is set aside for processes involving acid fumes, a third has steam baths and flash-proof fittings for the distillation of inflammable solvents. Several small laboratories have been provided for individual research workers; the physiology laboratory is, however, relatively large since cumbersome apparatus may be involved. There is a small workshop. A conference room is intended for staff meetings and teaching, and there are offices for the statistician and his assistants and for clerical staff.

The wards are pleasantly light and airy and there is a day room for patients and a night nursery. A concrete float is incorporated in the roof of one room so that if air-conditioning to give a constant environment became essential the necessary machinery could be placed in the roof space. A large main kitchen serves 15 Section V beds on the floor below, as well as about 8 beds in the research unit. There is a small metabolic kitchen, with an adjacent office for the dietitian.

Professor Dugald Baird is Honorary Director of the Unit. He is assisted by the Honorary Deputy Director, Dr. A. M. Thomson, who holds the post of research lecturer in the Department of Midwifery, University of Aberdeen and who has considerable experience of research in preventive medicine. The whole-time members of the present scientific staff of the Unit include: an obstetrician with special experience of steroid chemistry (Dr. A. Klopper), a medical physiologist (Dr. F. E. Hytten), a sociologist (Dr. R. Illsley) and a statistician (Mr. W. Z. Billewicz). The medically qualified members of the whole-time research staff have clinical status with the Regional Board and all undertake some routine clinical duties. This allows obstetricians on the hospital and University staffs to spare



A–D : Offices.
E : Conference room.
F : Out-patient room.
G–P : Research laboratories.
Q : Routine laboratory
R : Balance room.
S : Chemical store.
T : Technicians' room.
U–W : 2-bed wards.
X, Y : Single-bed wards.
Z : Sluice room.
A′ : Dry closets.
B′ : Bathroom.
C′ : Weighing room.
D′ : Patients' day room.
E′ : Duty room.
F′ : Nurses' cloakroom.
G′ : Observation laboratory.
H′ : Special ward.
I′ : Linen store.
J′ : Nursery.
K′ : Dietitian's room.
L′ : Metabolic kitchen.
M′ : Main kitchen.
N′ : Food store.

FIG. 1

Floor plan of Obstetric Medicine Research Unit, Aberdeen, prepared by courtesy of Messrs. Pite, Son & Fairweather, Architects, London.

FIG. 2
Obstetric Research Unit of the Medical Research Council, Aberdeen (top floor).

more time for research. All graduate staff are accorded University facilities and privileges as honorary members of University staff. Thus, in practice, both clinicians and research workers participate actively in each other's work, a feature greatly helped by the fact that each group has the same Director and shares the same accommodation.

The Origins of the Unit

Studies of foetal and neonatal mortality made in Aberdeen during the war indicated that the physique and health and the social background of pregnant women are at least as important as standards of medical care in determining stillbirths and prematurity rates. Nutrition was considered to be of particular significance and, accordingly, dietary studies were started in 1949, with financial support from the Department of Health for Scotland. It was soon realized that many social and psychological factors other than nutrition could not be ignored, and the active interest of Dr. J. N. Morris (Director of the Medical Research Council's Social Medicine Research Unit) resulted in several workers with the appropriate expertise being seconded to work in the University Department of Midwifery in Aberdeen. Many field studies and epidemiological surveys of a defined population demonstrated the value of a well-organized clinical records system, and details of every birth in the City of Aberdeen since 1948 were summarized on punch cards. The systematic use of records has improved the standard of routine clinical case notes and has made possible much valuable epidemiological research. It should be mentioned here that integration of policies and procedures is unusually easy in Aberdeen, where all clinical activity in obstetrics has for many years been organized as a single unit.

Laboratory research grew more slowly, due to limited facilities, but beginnings were made in 1950. Studies of breast feeding including chemical analyses of breast milk were undertaken and foetal oxygenation was also investigated, especially in relation to the phenomena of postmaturity.

In 1953, the system of dual control was ended, M.R.C. staff hitherto seconded from the Social Medicine Research Unit in London being attached directly to the Aberdeen University Department of Midwifery, and in 1954 the Medical Research Council offered to assimilate all research personnel working in the Department into a new Obstetric Medicine Research Unit.

Future Research

Most of the work undertaken in the past has been epidemiological in character and the volume of this kind of research is not expected to diminish. Work has so far been on primigravidae but it is hoped in future to study in more detail the problems of the multiparae, and to follow selected groups of primiparae through their subsequent reproductive history. The records are, of course, used routinely to assess the value of changes in treatment. Social problems arising directly out of specific clinical difficulties will continue to be investigated but the sociology of marriage, childbearing and family life will also be studied in its own right.

Surprisingly little systematic information is available on the physiology and metabolism of normal pregnancy, especially of a kind which will explain the differences of physiological efficiency as between one patient and another. It is hoped to study changes of body fluid and blood volumes during normal and abnormal pregnancy, and metabolic investigations may also be started. Studies of electrolytes during pregnancy have already been initiated by Dr. Ian MacGillivray, Senior Lecturer in Midwifery, using radioactive isotopes of sodium and potassium.

The advances in basic knowledge of the sex hormones and in the methods of measuring them which have been made in the M.R.C. Clinical Endocrinology Research Unit (Edinburgh) and other centres offer new tools for clinical research. The clinical and laboratory facilities now available in Aberdeen will enable these methods to be applied in the study of various obstetrical and gynaecological conditions.

Conclusion

The establishment of the Obstetric Medicine Research Unit and the provision of special laboratory and clinical accommodation for it

in the framework of a busy teaching unit and a University Department represents a new departure in obstetrics, at least in Britain. The keynote is intimate collaboration between practising clinicians and research workers with a wide range of interests and qualifications. Steady progress has come to depend increasingly on team work between experts commanding a wide range of techniques. The structure of the Unit permits long-term research plans to be made and carried out in a way which is virtually impossible with staff who, for lack of time and conflicting interests, can engage in research only on a limited scale. The human reproductive span is long and complex, and in view of its importance deserves sustained and versatile investigation.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

A MEETING of the Council was held in the College House on Saturday, 27th September, 1958, with the President, Professor A. M. Claye, in the Chair.

Professor G. Shedden Adam of Brisbane, Australia, was appointed Bernhard Baron Travelling Scholar for 1959.

AT an Extraordinary Meeting of Council held in the College House on Friday, 26th September, 1958, with the President, Professor A. M. Claye, in the Chair, the following were admitted to the **Membership:**

Prabhavathy Aiman.
Prasannatissa Harischandra Amarasinghe.
David Thomas Cecil Barber.
Carl Theodore Herzl Barrett.
Walter Philip Bonnici.
John Breeze.
John Michael Brudenell.
Donald Pui-Chee Chan.
Hermanus Johannes Hendrik Claassens.
Cecil John Tainton Craig.
Dilip Ranjan Das.
Robert Morrison Davie.
Richard Francis Drake.
Graeme Ross Duncan.
Diana Edwards.
George Herbert Ellidge.
Wellege Hemachandra Fernando.
Leonard Henry Fienberg.
James MacDougal Graham Harley.
Denys Heginbotham.
James Bleakley Hemsley.
Alice Hsiang-Lien Hsu.
Trevor Rhys Hunt.
Peter John Huntingford.
Sylvia Ray Ingold.
Katherine Isobel Jack.
Robert Douglas Johnstone.
Ellis William Parry Jones.
Anthony John Keane.
Arthur Charles Keast.
Denis Malcolm Davies King.
Sybil Vera Kinley.
Daphne Rae Lowe.
John McGlone.
Sheila Malhotra.
Denis Thorpe Mathews.
Charu Chandra Mitra.
William Peter Lochrane Morrison.
Alexander Desmond Muirhead.
Salvino Muscat.
Isabella Ross Napier.
Hannah June Pash.
John Herbert Peters.
David Walter Pfanner.
Denzil Mervyn Reader.
Walter Joseph Cyril Rebello.
John St. George.
Peter Cameron Stichbury.
Jean Orr Struthers.
William Moss Elvery Tweed.
Radha Naravan Udipi.
Thiagarajah Visvanathan.
Alistair William Goold Weir.
Dorothy June Whitney.
William Geoffrey Wicks.
Balasubramaniam Yoganathan.

REPORTS OF SOCIETIES

TRANSACTIONS OF THE GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

February 1958

A Meeting of the Glasgow Obstetrical and Gynaecological Society was held in the rooms of the Royal Faculty of Physicians and Surgeons, Glasgow, on Wednesday, 19th February, 1958. The President, Professor D. F. Anderson, was in the Chair.

Mr. T. L. T. Lewis addressed the Society on the

Potential Dangers of X-rays in Pregnancy

The speaker said that as a result of the harnessing of atomic energy for peaceful and warlike purposes groups of scientists have been called together to review the biological effects and possible dangers to man of the radiation released. In this country the Medical Research Council issued a report, *The Hazards to Man of Nuclear and Allied Radiations*, and in America the National Academy of Sciences published a report on *The Biological Effects of Atomic Radiation*. In both these reports the contribution to artificial radiation by diagnostic X-rays is stressed. He thought it would be profitable to examine the evidence for believing that X-rays in pregnancy were dangerous, and began by saying that there were two doses of irradiation which had to be kept in mind. The first was the dose received by the maternal gonads and the foetal gonads during an X-ray examination such as pelvimetry and the second was the gonadal dose received as the result of natural background radiation.

Evidence was produced to show that in one generation the dose received from the natural background is approximately 3 r. The dose from one pelvimetry examination is about 2·7 r and the dose being received from diagnostic radiology on average in this country is in the order of 0·75 r to the gonads of each person in a generation.

Mr. Lewis then considered the harm that could be caused by exposing pregnant women to X-rays under the following headings:

(1) *Direct injury to the mother.*
(2) *Direct injury to the foetus.*
(3) *Subsequent leukaemia in the foetus.*
(4) *Genetic damage.*

There is no evidence that any direct injury to the mother is likely to come from the dose given in diagnostic radiology. The work of Court-Brown and Doll, however, suggests that leukaemia in the mother could be caused by irradiation of the bone marrow; except in very early pregnancy direct injury to the foetus producing abortion, stillbirth or congenital deformity is very unlikely in the dose required in diagnostic radiology.

The lecturer then dealt with the problem of subsequent leukaemia in the foetus. He quoted the work of Alice Stewart and her co-workers in Oxford and he reported on a group of over 2,000 patients who had been X-rayed during their pregnancy and who had been followed up afterwards. In not a single one of these cases had the child developed leukaemia up to the age of ten years. He thought that the risk of leukaemia developing as the result of diagnostic radiology if continued at the present rate in this country would be about one case in forty thousand births. It was stressed that this had to be compared with the present perinatal mortality rate of about fourteen hundred in forty thousand births.

The possibility of genetic damage from diagnostic X-rays is very difficult to assess. The risk is that of any increase in the rate of mutations the majority of which are harmful. The gonads probably need a dose of 30 to 80 r for the mutation rate to be doubled. This carries with it a very small risk to the individual, perhaps 1 in a 1,000 chance of bearing a harmfully affected child. It is probably safe for up to 1/50th of the population to be exposed to a dose of radiation of this order. However, if reckoned over the population as a whole a dose in excess of this would be harmful.

Mr. Lewis then made suggestions for reducing the amount of exposure during diagnostic X-rays in pregnancy.

THE EAST ANGLIAN OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

March 1958

A meeting of the Society was held in the Drummond Hall at the West Suffolk Hospital on Saturday, 22nd March, 1958. On this occasion local general practitioners and midwives were invited to attend to hear the views of a "Brain Trust", formed by senior members of the Society, on a number of questions previously submitted to the Question Master—Mr. O'Meara.

At the end of the meeting our President, Mr. Bulman, reviewed the discussion as follows:

The questions covered many problems of importance to general practitioners and in domiciliary midwifery, and the various views expressed in the answers showed that there was still no consensus of opinion concerning many of the points raised. A question concerning the use

of Ergometrine in the second stage of labour produced considerable discussion, with a majority of the panel in favour of its use. Those against the routine administration of Ergometrine in this way pointed to the difficulty of correct timing in some cases and to the risk of retention of the placenta, which might call for manual removal, and it was suggested, for the latter reason, that those making use of this treatment should be familiar with the technique of manual removal in such cases as might require it.

A further question concerned the length of time it was considered safe to leave the placenta in the uterus. It appeared that no member of the panel was prepared to leave the placenta for more than one hour, unless circumstances were very exceptional. The majority of the panel favoured earlier removal, as a means of avoiding the shock which was liable to occur in certain cases of delay in delivery of the placenta. It was also pointed out that even if there was no obvious bleeding, a retroplacental loss might be taking place, as a result of which an undesirable amount of blood might be lost to the patient, though the fact that it was taking place was not recognizable by the attendant.

The panel had no very decided views on the value of ovarian extracts in cases of threatened or habitual abortion. On the whole they seemed to agree that such value as these preparations might have seemed to be at least as much psychological as physical.

A further question on the use of hormones in cases of menstrual irregularity produced a majority opinion that there was too great a tendency to use hormones and that in many cases they were either unnecessary or undesirable.

The future of domiciliary midwifery came in for a certain amount of discussion, as the result of a question suggesting that the future outlook for domiciliary midwifery was very poor. With this view the panel did not agree, though it was pointed out that various changes in the present system would probably be brought about in the comparatively near future and might well result in better conditions for the practice of domiciliary midwifery, but would certainly not lead to its extinction.

On the question of the treatment of acute inversion of the uterus, the general feeling was that this should be treated as rapidly as possible, by the means necessary to overcome the severe shock and by such methods of replacement of the inversion as were possible in the circumstances.

Further questions dealt with included a brief discussion of A.I.D., in which almost all the team disagreed with this procedure.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

March 1958

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Sheffield on 21st March, 1958. Professor C. S. Russell was in the Chair.

Mr. R. F. Lawrence reported two cases of

Utero-Colic Fistula

The first patient, a woman of 81, had been seen 2 years earlier when an offensive vaginal discharge was noticed. Later she was admitted to hospital as the discharge had become faecal. Apart from laparotomy for a benign ovarian tumour, there was nothing significant in her past history.

She was a frail woman, though there was no evidence of recent loss of weight. The vulva was ulcerated from faecal contamination, but vaginal examination showed the vaginal wall intact and the cervix normal with the uterus freely mobile and the fornices clear. A left inguinal colostomy was never wholly successful, and a barium enema showed diverticulosis, and the barium flowed readily to the colostomy. At laparotomy adhesions were found between the pelvic colon and the uterus and there was a multilocular cyst of the left ovary. The cyst was removed and a transverse colostomy performed, but though there was temporary improvement, she died 3 months later. At post-mortem both uterus and colon were found infiltrated with carcinoma which appeared to have origin in the bowel.

The second case, a woman of 56, was seen in June, 1954, because of vaginal bleeding for 4 weeks. Nothing abnormal was detected on vaginal examination, but curettage produced suspicious looking material. Section of the curettings confirmed the malignancy, and as the patient refused operation, radium was inserted. Ten months later she was seen again because of a profuse faecal discharge, but no recto-vaginal fistula could be located. Because of her intolerable condition she was willing to accept anything that would afford relief. At laparotomy the caecum and terminal ilium were found to be adherent to the right cornu of the uterus. The adherent intestine was removed, and an end to end anastomosis performed. An attempt at total hysterectomy proceeded normally till the uterine arteries had been divided, when the junction of the corpus and the cervix began to tear. A course of deep X-ray was given, and she survived 3 years.

Discussion

Professor C. S. Russell thought a transverse colostomy was preferable, but he asked for discussion on what treatment could be offered to these patients.

Mr. T. Smith had cared for an old lady of 76 who at first noticed a serous discharge. The history suggested acute diverticulitis. A curettage produced no malignant material, but later food particles were found in the discharge and an X-ray showed a long track from the uterine fundus to the pelvic colon. Advice on diet offered sufficient relief as she was thought too frail for surgery.

Mr. D. H. Lees had performed a curettage in a woman who later became acutely ill so that it was thought the uterus had been perforated. Adenocarcinoma arising in bowel was reported, and she developed a fistula. She died from generalized carcinomatosis.

Miss U. M. Lister reported a similar case occurring in a woman of 73. She had been well until 3 weeks before when sudden abdominal pain developed and soon afterwards a discharge which became offensive. There had been constipation for 1 week and vaginal bleeding for 1 day prior to admission. Faeces were found coming through the cervix, and a barium enema demonstrated a long track. At laparotomy it was found that the carcinoma of the pelvic colon had become adherent to the left tube and faeces were discharged via the tube and uterus. The patient died soon after removal of the pelvic colon and uterus.

Dr. D. H. Blakey read a short paper on

THE TREATMENT OF BARTHOLIN'S CYSTS BY MARSUPIALIZATION

(This article appears on page 800 of this issue)

Discussion

Mr. C. R. MacDonald had been shown this operation in the States. He had never seen dyspareunia develop from lack of secretion from the scar after excision of a cyst as he made the incision on the outside of the labium. He did not think the aetiology of Bartholin's cysts was clear.

Dr. R. Newton had seen very few complications from excision, but intended to do this operation to see if the presence of the fistula causes soreness. If it can be done on a Bartholin abscess in the Out-Patient Department it was worth trying.

Mr. L. B. Patrick found marsupialization a very useful operation when the waiting list was long.

Mr. C. J. Dewhurst was not impressed by the need for the gland to remain functioning, but simplicity was the advantage of this operation.

Mr. F. Stabler thought that Bartholin's duct was not cut during colporrhaphy, but injury was common with lateral episiotomy.

Mr. R. F. Lawrence had performed a similar operation on small vaginal wall cysts with good results.

In reply Dr. Blakey said that the main merit was in the extreme simplicity. The Bartholin duct was not damaged in colporrhaphy, but with chronic infection there may be partial and gradual blockage. Marsupialization was only possible if a cyst was present, and not with a hard knot of fibrous tissue.

Mr. D. H. Lees and Dr. C. G. Paine presented a paper on

LIPOID MASCULINIZING TUMOURS OF THE OVARY

(This article appears on page 710 of this issue)

Discussion

Professor C. S. Russell expressed his appreciation of the detailed presentation of the case.

Mr. R. B. Wright found the paper most interesting as he had seen a similar case. The patient, a woman of 44, had been referred because of a beard, harsh voice and slight enlargement of the clitoris. The right ovary was just palpable, and at laparotomy a small bright yellow tumour was found. There was good recovery with retrogression of signs and return of menstruation, but what was most marked was the change in personality from depression to cheerfulness in one week, and so great was this at the follow-up review that the patient was unrecognizable.

Mr. F. Stabler congratulated Mr. Lees and Dr. Paine as there had been no case described with ascites of this degree. He had recorded a case in 1939. Symptoms began at the age of 17—hirsutes, amenorrhoea, enlarged clitoris and a base voice. There was a prolonged period of defeminization before evidence of masculinity. There was also a change in demeanour from a dull, hang-dog look to cheerfulness. The only other case he had heard of had been in a girl of 16 in South Shields who grew a big, bushy, ginger beard. He went at once to the hospital, but they had thrown the tumour away.

Mr. L. B. Patrick enquired about the sexing of the cells.

In reply Mr. Lees said he would never hope to defeat the North of England. As in Mr. Wright's case, the change in personality had been very marked. She was convinced she would die and so decorated the house to make it comfortable for her husband. The customers at her husband's shop thought he had married again. The voice change was not noticeable, and there had been a period of defeminization first.

Dr. Paine did not know of reports of the sexing of the cells in these tumours, and he thought observations on sexing worth collecting. In Turner's syndrome many patients were genetically males.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

APRIL 1958

A Meeting of the North of England Obstetrical and Gynaecological Society was held in Leeds on 18th April, 1958. The President, Dr. E. A. Gerrard, was in the Chair.

Dr. J. M. B. Muirhead presented a case record of

A LARGE CERVICAL FIBROID

Mrs. R.G., aged 46, was admitted to hospital during the evening of 28th January, 1957, because of acute retention of urine. For 4 weeks prior to admission she had experienced difficulty in starting micturition, and that morning the difficulty had been more than usual. Menstruation was regular, the loss scanty and the last 34 days prior to admission. Her 4 confinements had all been normal, the youngest child being 9 years old.

Abdominal examination showed a grossly distended bladder from which 40 ounces of urine were released by catheterization. A firm irregular tumour could then be

felt rising from the pelvis to the level of the umbilicus. Vaginally a large tumour was found filling the pelvis and displacing the posterior wall forwards so that the cervix could not be identified.

At operation the tumour proved to be a solitary fibroid arising in the cervix posteriorly and central in position. The uterus was perched on top of it, and the bladder was raised out of the pelvis. Myomectomy was performed before proceeding to an easy hysterectomy. The vagina was greatly distended, and the posterior wall much elongated. To reduce its size a cuff of vagina was excised in addition to a triangular area from the posterior wall. The fibroid was oval in shape and measured 15 by 10 centimetres.

After 6 weeks the appearance of the vagina was normal although rather capacious at the vault, and when seen 4 months later a mis-shapen cervical stump was found. A biopsy taken from what seemed to be an incomplete external os showed squamous epithelium only.

The two interesting features of this case are the history of difficulty in starting micturition only in the morning, and the site of origin of the fibroid in the cervix. It was thought that the fibroid arose in the supra-vaginal cervix and by its growth elongated the canal and stretched it from side to side. The vaginal portion of the cervix became so thinned by this expansion that it was indistinguishable from the vaginal walls.

Discussion

The President commented on the advantage of myomectomy before hysterectomy and on the removal of a triangle of vaginal wall to reduce the size of the vagina.

Mr. T. B. FitzGerald had found it useful to do an abdominal colporrhaphy if hysterectomy had to be done by this route. He thought the cervix might have been grossly stretched, and shut down again as it does after pregnancy.

Miss E. M. Mills had seen a case of marked stretching of the vagina by an enormous polyp. After removal of the polyp by morcellement the vagina shrunk so that it would not admit a pencil. She questioned if the repair of the distended vagina was necessary.

Mr. G. W. Theobald was disappointed no one had yet mentioned a bigger fibroid. He thought the fibroid grew from the vaginal portion of the cervix with the little uterus pushed up on the top.

Mr. E. E. Rawlings recorded a similar case, the fibroid reaching above the level of the umbilicus.

Mr. C. J. K. Hamilton described a "mere pimple" of 32 pounds. He agreed the fibroid arose from the vaginal portion and advised an intravenous pyelogram in this type of case.

Mr. H. Agar commented on the way most large fibroids protruded into the vagina so that it is difficult to tell if the tumour is a polyp.

Professor C. S. Russell asked about cervical fibroids and pregnancy. At Caesarean section they may distort the lower segment and cause much bleeding. He wondered if anyone had done a deliberate myomectomy in pregnancy.

Mr. J. F. Redman had seen a woman who extruded a fibroid after normal delivery. He thought myomectomy in pregnancy dangerous.

Mr. P. C. Steptoe had performed an easy vaginal myomectomy at the 32nd week of pregnancy. Delivery later was normal. She had noticed difficulty in micturition and as the tumour was so accessible it was a great temptation. He also mentioned a case in which bladder distension resulted from gross constipation.

Mr. L. Snaith and Mr. L. B. Patrick both thought that in most cases fibroids situated low down became drawn up above the presenting part as pregnancy advanced.

Mr. R. B. Wright mentioned a very small fibroid which growing inwards to obstruct the cervical canal produced such severe dysmenorrhoea that the patient was admitted as an emergency.

Mr. F. DaCunha had removed a fibroid in a case where pregnancy was unsuspected. Delivery later was normal.

Dr. J. C. S. Leverton read a paper on

Some Aspects of Ovarian Conservation at Hysterectomy for Benign Conditions

Though there had been a trend towards conservation there is no agreement with regard to conservation of the ovaries at the time of hysterectomy. In the present small series of 372 cases the results were suggestive rather than dogmatic. There was still no agreement as to the age at which it was proper to remove normal ovaries, and opinion was divided as to the incidence of subsequent ovarian carcinoma. Conserved ovaries were thought to remain functioning for 2 to 3 years, and views were divided about the severity of the climacteric if the ovaries were removed, or if one ovary conserved was as good as both.

Amongst some 70 papers on this subject there were 12 in which the radical approach was advocated. Hot flushes were used as the indication of ovarian failure. It was thought that the hot flush was an erroneous indication of ovarian failure, and in this investigation the following methods were used: (1) symptomatology, (2) basal temperature charts, (3) gonadotrophin and pregnanediol assays, (4) vaginal smears and (5) vaginal pH.

All the patients were 44 years of age or less at the time of hysterectomy. In 144 cases of bilateral conservation 28·5 per cent experienced hot flushes but only 18·1 per cent developed the full climacteric syndrome. Of 97 cases of unilateral ovarian conservation 49·5 per cent developed hot flushes and 40·2 per cent the full syndrome. Maxwell in 1924 indicated that post-operative flushes were worse if the haemoglobin was below 70 per cent, and in 30 cases in the present series there was the same finding.

Bilaterally conserved ovaries functioned adequately for about 7 years in 80 per cent of cases, but the figure was lower for unilateral conservation.

Age did not appear to affect the severity of the climacteric syndrome, but cases exhibiting high pre-

operative oestrogen levels such as metropathia haemorrhagica, had a more severe climacteric. There was no evidence that ablation gave a short sharp syndrome.

Unilateral oöphorectomy seemed often to have been undertaken unnecessarily, in 68·6 per cent of the cases normal ovaries being removed. There was great divergence of opinion concerning pathological changes developing in conserved ovaries, and none had been found in the series under review. In a small number of cases where tension was put on the infundibulo-pelvic fold there was evidence of ovarian failure and a significantly higher number of immediate post-operative climacteric disturbances.

In women who had undergone bilateral ablation 28·2 per cent of women experienced monthly cyclical phenomena. Temperature charts showed good function where both ovaries were conserved, but in the majority no ovulation pattern with only one ovary. There was little evidence that bilateral ablation led to early weight increase.

Pregnanediol and gonadotrophin assays were performed in 33 patients. With bilateral conservation most gonadotrophin levels were low, a few high figures possibly representing ovulation peaks, but these peaks were more frequent with bilateral than unilateral conservation. With regard to pregnanediol, there were the expected number of high figures with bilateral conservation, fewer with unilateral conservation, and none with bilateral ablation.

Vaginal pH and smear were not reliable indications of ovarian failure. In a number of cases of bilateral ablation there was good cornification and vaginal acidity.

Discussion

The President felt that the most significant point was that half these women received oestrogens and this might have affected the results.

Mr. T. F. Redman commented on his impression that there was not much difference between those who did and did not have the ovaries removed. He had seen 1 case of subsequent ovarian carcinoma. Patients should remain under observation to see if they require oestrogens.

Mr. H. Malkin now removed the ovaries as a friend of his had developed carcinoma in an ovary conserved at hysterectomy.

Many members of the society had also seen ovarian carcinoma following hysterectomy.

Mr. L. B. Patrick thought many people were irrational in this. We worry about leaving them at abdominal hysterectomy, and do not if the hysterectomy is vaginal. Often at vaginal hysterectomy the pedicles were pulled down to the vaginal vault. When in Boston he had found the policy to be to castrate all women and give them 0·05 mg. ethinyl oestradiol if necessary for 20 years.

Mr. L. M. Snaith thought the question of immediate oestrogen therapy should have been investigated. Questions had been asked at the end of the investigation and this was not so reliable. He also wished to know for how long the hot flushes continued.

Mr. G. W. Theobald mentioned that libido can remain many years after removal of both ovaries.

Professor C. S. Russell and Mr. C. J. Dewhurst showed two films

SOME UNUSUAL GYNAECOLOGICAL CONDITIONS

TWO CASES OF INTERSEX

These films were made for teaching undergraduates and recent graduates.

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY AND GLASGOW OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

MAY 1958

A combined Meeting of the North of England Obstetrical and Gynaecological Society and the Glasgow Obstetrical and Gynaecological Society was held in Glasgow on 2nd May, 1958. The Presidents, Professor D. F. Anderson and Dr. E. A. Gerrard, presided.

Dr. D. C. A. Bevis opened the discussion on

ACCIDENTAL HAEMORRHAGE

For the purpose of this paper accidental haemorrhage has been considered to be ante-partum haemorrhage associated with retroplacental clot and without evidence either before or after delivery of praevia implantation or associated pathology.

Park Hospital, Davyhulme, draws from a population of about 322,000 living in conditions varying from rural and residential to heavily industrialized slums. The incidence of hospital delivery varies from 25 to 85 per cent in different areas, and the majority of abnormal cases come to the main unit at Park Hospital.

In the 6 years 1952 to 1957 there were 8,075 deliveries in hospital, 108 of these being associated with accidental haemorrhage, an incidence of 1·3 per cent. Accidental haemorrhage accounted for 16·6 per cent of the 313 stillbirths and 3·4 per cent of the 204 neonatal deaths. Comparable figures are given in the Maternity Reports for the Manchester Regional Hospital Board. This incidence is higher than in other published series and it is possible that environment plays a part as all the cases came from the industrial area.

The incidence in booked and non-booked cases (51 and 57) is almost the same, and the results for the baby are identical, 26 stillbirths and 27 babies under 5½ pounds in both groups. Although surgical induction of labour was often used, this did not account for the incidence of small babies.

Only 36 patients showed evidence of pre-eclampsia, 4 other patients had hypertension and there was 1 case of chronic nephritis. Pre-eclamptic toxaemia increased the foetal mortality to 67 per cent compared with 22 per

cent for the non-toxaemic group. In this series 30 patients (27·8 per cent) had a haemoglobin concentration of less than 65 per cent and of these 12 had pre-eclampsia.

Study of the ages showed that 75 per cent were under 35 and 17 per cent between 35 and 40. Comparison with the Registrar General's figures for age at delivery showed a distinct difference, the probability of this difference arising by chance being less than 1 in 1,000. The analysis for parity showed a similar variation: 28 per cent were primiparae and 61 per cent had had between 1 and 4 previous pregnancies. Both these results are contrary to those reported in the literature, but in Lancashire the young multipara is the one most likely to develop accidental haemorrhage.

These patients are also somewhat infertile, and there was a higher incidence of previous unsuccessful pregnancies than in the other patients admitted to hospital for delivery.

Treatment was mainly traditional. After resuscitation and when the uterus began to recover its tone the membranes were ruptured. A pitocin drip was not used in this series. Delivery was usually rapid, no patient taking more than 24 hours. Only 10 had any degree of post-partum haemorrhage, and there was no case of hypofibrinogenaemia. Caesarean section was carried out 5 times, 3 of the babies later dying.

There does not seem to be any clinical guide to indicate which patient will develop an accidental haemorrhage. Further it is difficult to tell which patient is going to come to harm. The foetal mortality also is appalling, and although 33 of the 52 stillbirths in these 108 patients were dead on admission, there was failure to salvage the other 19, and a further 7 babies died in the neonatal period. Perhaps Caesarean section should be employed more frequently.

Mr. T. A. Tennent read the second opening paper on

Hypertension in Accidental Haemorrhage

It is proposed to consider the significance of hypertension in severe accidental haemorrhage and to suggest a possible course of management when this complication occurs. The series under review comprises 162 consecutive cases treated at the Maternity Hospital, Bellshill, in the 8 years 1950 to 1957 during which time there has been a single policy of treatment. Only cases of mixed or concealed accidental haemorrhage where there was indisputable evidence of placental separation are included and where the degree of placental separation has been enough to produce foetal death, or a crater of considerable size or that the actual separation and bleeding were observed in a normally situated placenta at Caesarean section. In these 162 cases only 21 infants were born alive, 17 being delivered by Caesarean section.

Records of blood pressure, haemoglobin, occurrence of shock and renal function were kept. Daily blood ureas were taken, and the urinary output and specific gravity estimated. The most useful guide to the severity of the condition was the blood urea. Where it rose above 50 mg./100 ml. but not above 100 mg. in the first week the case has been classified as mild, there were no symptoms and oliguria was transient. In the severe case the blood urea rose above 100 mg. in the first week.

The three most important advances in the treatment of accidental haemorrhage are adequate blood replacement, correction of fibrinogen deficiency and the rational treatment of renal failure.

In the acute phase blood transfusion was used liberally to keep the haemoglobin above 70 per cent (Sahli). The average transfusion was 2 litres, but one case required 8½ litres.

The "Fibrindex" test has been used in all cases, and where fibrinogen deficiency has been discovered a transfusion of double strength plasma was given. Since 1956 there were 17 cases of fibrinogen deficiency in 54 cases of accidental haemorrhage, and 2 of the deaths in the series were probably due to afibrinogenaemia.

For renal failure the regime indicated by Bull, Joekes and Lowe (1949) was followed. Of 18 severe cases 3 died and all showed renal cortical necrosis at autopsy.

In the first 3 years of this series there had been only 1 death from shock, but 3 deaths from renal failure. Renal failure was found in 39·7 per cent of cases, nearly half of them severe, and the association between hypertension and renal failure seemed convincing. A blood pressure of 140/90 mm. Hg was taken as evidence of hypertension. In 58 cases up to 1952, 36 showed hypertension with an incidence of 25 per cent of severe renal failure and 3 deaths. In the remaining 22 of normotensive patients the incidence of severe renal failure was 4·5 per cent and there were no deaths.

From 1953 to 1957 efforts were made to minimize the effects of hypertension, and in 104 cases of accidental haemorrhage there were 57 hypertensive cases with 10·5 per cent showing severe renal failure, but no maternal deaths. The normotensive patients gave an incidence of severe renal failure of 4·2 per cent.

Since 1953 bromethol has been used in cases of hypertension, and Caesarean section employed more freely for pre-eclamptic toxaemia. Renal cortical necrosis may occur in eclampsia, and shock or collapse from haemorrhage may have a similar effect. As hypertension and haemorrhage collapse operate in accidental haemorrhage, renal failure should be a fairly common occurrence. It has been the standard practice in severe accidental haemorrhage to resuscitate the patient by blood replacement, then rupture the forewaters, and if the blood pressure rises above 150/100 mm. Hg to give 4 to 6 ml. of bromethol per rectum. Blood replacement and correction of fibrinogen deficiency are maintained until delivery.

With this management the incidence of severe renal failure has been reduced to 7·7 per cent in the 104 cases in comparison with 17·2 per cent in the 58 cases prior to 1952.

Caesarean section has been used on only 3 occasions in the management of accidental haemorrhage, but more frequently for foetal distress and severe pre-eclampsia. It seems probable that this more radical approach to severe pre-eclampsia has had a favourable influence on the figures for accidental haemorrhage.

It now seems that there is hope that the problem of the maternal mortality in severe mixed and concealed accidental haemorrhage is near a solution. The incidence of severe renal failure has been reduced by half, and these results have been achieved by conservative therapy and a few prophylactic Caesarean sections. The section should be done before any major degree of separation has occurred.

The problem of foetal mortality is more difficult. The only hope seems to be to perform Caesarean section in the few cases of pre-eclamptic toxaemia where there is some warning. Perhaps the early detection and prevention of pre-eclamptic toxaemia between the 20th and 30th week may have an influence, and research should be directed to the aetiology of placental separation.

Mr. C. J. Dewhurst mentioned the work done in Sheffield on pregnanediol excretion in normal pregnancy and also in cases of accidental haemorrhage. In the cases studied before the haemorrhage, the pregnanediol values have fallen either within the normal range or below it. A normal pregnanediol excretion does not exclude the possibility of an accidental haemorrhage, but if the levels are low the risk to the child is increased. Most of the cases showing low levels have evidence of pre-eclamptic toxaemia or hypertension, and it seems clear that the child was in danger, though the urgency of the problem is more difficult to assess. An example of this was a patient whose pre-eclamptic toxaemia settled so rapidly that she was discharged home despite low pregnanediol levels. Next day she had an accidental haemorrhage. Perhaps in this type of case where there seems no cause for alarm the pregnanediol excretion would be of value in showing up the poor placental function. After an accidental haemorrhage in which the child survived the pregnanediol excretion falls in the normal range, but, where low levels were obtained after the initial haemorrhage and before death of the child, the urgency of the problem is underlined. If pregnanediol values in the order of 10 or 12 mg. per day are obtained in association with a small child Caesarean section has a place in treatment, and in patients with poor obstetric histories the pregnanediol excretion might help to assess placental function.

Dr. F. DaCunha reviewed cases of accidental haemorrhage occurring at Oldham General Hospital (1953–1957) and Ashton General Hospital (1953–1956). Only cases with a retroplacental clot were included. There were 92 cases (0·72 per cent of all admissions) with 52 stillbirths and 3 neonatal deaths. Emergency cases occurred twice as often as booked cases, but the results were the same in both. In 38 cases there was shock and evidence of intrauterine death, but in the remainder the child was alive on admission or showed distress in labour.

Afibrinogenaemia was seen in only 2 cases but pre-eclamptic toxaemia was present in half the cases. Caesarean section seemed to give better results than vaginal delivery, and where the heart was still audible on admission death occurred before vaginal delivery was accomplished.

Evidence of pre-eclamptic toxaemia was present in 11 of the 17 booked patients at the attendance preceding their admission to hospital. Immediate admission might have influenced the results. Accidental haemorrhage was commoner in women under 30, and in those who had had not more than 3 children.

Dr. J. F. Kerr Grieve confined his remarks to antenatal care. He referred to 41 cases of accidental haemorrhage with a foetal loss the same in booked and unbooked patients, but the incidence of accidental haemorrhage was lower where antenatal care had been given. He then outlined the diet given to each patient, the repeated blood counts and careful weight charts which showed up defaulters. With careful control patients with bad obstetric histories carried through, and the ravages of pre-eclamptic toxaemia and accidental haemorrhage were prevented.

Mr. W. Calvert did not think weight gain helped to find the candidate for accidental haemorrhage. They do not develop oedema, and he had one case who lost 2 pounds just prior to the haemorrhage.

Dr. J. S. Scott asked for the method of fibrinogen replacement. As there was usually a deficiency of many factors, plasma was better than fibrinogen. The term afibrinogenaemia was best dropped for coagulation failure.

Dr. J. W. Chambers usually saw the aftermath. He had records of 42 cases, 8 required the modified renal failure routine and showed rises in blood urea, and 3 developed acute renal failure. The blood urea might rise to 100–200 mg. despite good urine output.

Mr. L. Snaith had abandoned weight recording in 1942 but later started again. He found a correlation between excessive weight gain and small placentae especially round the 24th week of pregnancy.

Dr. H. MacLennan commented that the debate had gone from treatment to weight gain. In private practice and hospital the incidence of placenta praevia is the same, but accidental haemorrhage is less frequent in private practice. The incidence may vary in different areas where standards are not the same, and it seemed commoner in the undernourished and anaemic.

Dr. J. M. McBride said that in his experience not many babies were saved by Caesarean section. It was usually a transfer from the stillbirth to the neonatal column.

In his reply Dr. Tennant mentioned first that he used double strength plasma to control clotting defects. He was convinced of the value of bromethol, and his improved results were not due to rupture of the membranes. It was only an impression that these patients were more anaemic, and a long-term controlled experiment would be needed to prove this.

HOSPITAL REPORTS

BY

JOHN S. TOMKINSON, M.B., F.R.C.S., M.R.C.O.G.

THE CLINICAL REPORT OF THE ROTUNDA HOSPITAL, DUBLIN, FROM 1ST NOVEMBER, 1955, TO 31ST OCTOBER, 1956

IT is always a pleasure to receive this report for review and like its predecessors it amply repays a careful study. The report comprises an introductory account of the year's work by the Master, followed by departmental reports, statistical analyses of the extern and intern maternity services and then summaries of the tables, recommended by the Standard Reports Committee of the Royal College of Obstetricians and Gynaecologists each headed by an explanatory discourse. From these reports and accounts one has a good impression of the work going on at the Rotunda.

During the previous year alterations to the labour ward floor caused a reduction in the number of available beds. In the year under review the section under reconstruction was put into use and resulted in the record number of 4,456 intern deliveries. Against this must be set the falling number of extern deliveries (1,389), probably due to social conditions and the difficulty of obtaining home help.

On 1st May, 1956 alterations were made in the staffing arrangements at consultant and registrar levels. Each Master, on completing his 7 years term of office, is entitled to continue in an active and clinical capacity for a further 14 years and then ceases to remain on the active consultant list. In addition to the Master and the two ex-Masters at any given time, two junior consultant posts have been created. Another advance has been the formation of a liaison between the Hospital and the Medical School at Trinity College, Dublin, enabling the Professor of Obstetrics at the University to become an Honorary Consultant of the Hospital, having access to beds and Out-Patient clinics for teaching purposes in obstetrics and gynaecology. The posts of Assistant Master have been abolished, the two appointments being replaced by one Clinical Assistant and two resident Registrars.

The report records a further fall in the stillbirth rate (to 3·14 per cent) in intern deliveries. Whilst no maternal deaths occurred in the extern service of the hospital, 5 took place in the hospital and these are fully recorded. One of these happened in a woman who had had an ante-partum haemorrhage at the 36th week of pregnancy, 2 weeks before admission; she bled severely at home the night before and shortly before a long car drive by her doctor to the hospital and died half-an-hour after admission after another severe haemorrhage. The Master lists six points of criticism about the management of the case before and after admission. Other cases died from Hodgkin's disease, from metastatic adenocarcinoma of the breast, from ? severe thrombo-cytopenia, and from miliary tuberculosis.

Three cases of uterine rupture are recorded. In one an internal version was performed in the patient's home because of a prolapsed cord with the cervix one-half to three-quarters dilated; she was admitted to hospital with the foetus undelivered and, soon after the after-coming head was perforated, further bleeding occurred and the patient was so shocked that a laparotomy was performed on the labour ward couch and a hysterectomy carried out, the patient surviving. In the second case, a forceps delivery secured a live baby (outside the hospital service), through the posterior lower segment of the uterus *via* the pouch of Douglas; it was probably a case of non-dilatation of the external os of the cervix with the head very low in the pelvis. She was admitted with a vaginal pack *in situ* and when this was removed the cervix and part of the lower segment prolapsed outside the vulva. This patient survived a laparotomy and suture of the rent. The third patient had an internal version for a prolapsed cord in a county hospital; the baby was dead-born, profuse bleeding occurred and intestine was seen in the vagina; a subtotal hysterectomy was performed in the Rotunda Hospital and she made an excellent recovery. The Master comments on the extreme danger of over-heroic and over-energetic management of cases of prolapsed cord.

THE OBSTETRIC UNIT MEDICAL REPORT OF THE MILL ROAD MATERNITY HOSPITAL, LIVERPOOL, FOR 1956

THE report consists mainly of a condensation of the tables recommended by the Hospital Reports Committee of the Royal College. This method of preparation together with the typescript and binding adopted have, doubtless, contributed to the commendable speed of publication. There is no mention of the number of beds available; the total number of deliveries was 3,465, one maternal death occurring from lobar pneumonia and long-standing bronchiectasis. The stillbirth rate was 3·16 per cent and the combined stillbirth and neonatal death rate was 5·2 per cent.

The incidence of pre-eclampsia, essential hypertension and chronic nephritis was 6·6 per cent and 4 cases of

eclampsia were treated. Seventeen cases of placenta praevia were admitted and treated by Caesarean section (no mention of type of operation) in 10 instances and the remainder *per vaginam*. Kielland's forceps rotation and delivery was accomplished in 115 cases of persistent posterior position and transverse arrest of the occiput out of a total of 149. The foetal mortality in uncomplicated breech deliveries was 2·2 per cent; forceps to the after-coming head was used in 68 out of 89 cases. Of the 54 patients in labour following a previous Caesarean section, 50 were delivered vaginally (92·5 per cent). A "trial of forceps" with full preparation for Caesarean section was carried out on 18 occasions, a section being performed in 7 cases.

The incidence of post-partum haemorrhage was 4·4 per cent and that of manual removal of the placenta 0·9 per cent. A surgical induction of labour was done in 6·8 per cent of patients delivered, the main indications being maturity or postmaturity in 133 and pre-eclampsia or hypertension in 79 instances from a total of 239. The Caesarean section rate was 3·2 per cent (112 cases); all but 2 were lower uterine segment sections. The forceps delivery incidence was 9·8 per cent.

Two cases of special interest are described; one a case of accidental haemorrhage complicated by anuria, the patient recovering and becoming pregnant again; the other, a case of rupture of a degenerating fibroid the size of a foetal head which was removed during pregnancy (the pregnancy continued, but later a twin pregnancy was diagnosed, the patient developed pre-eclampsia and intra-uterine foetal death occurred).

This is an interesting report but because of its brevity information has been omitted which would have been of value. In a hospital with a large number of deliveries per annum, a table of comparative statistics is a useful indication of progress.

THE MEDICAL AND CLINICAL REPORT OF THE ROYAL WOMEN'S HOSPITAL, MELBOURNE, AUSTRALIA, FROM 1ST JULY, 1954 TO 30TH JUNE, 1955

THIS report is published as three bound volumes of typescript. The first 20 pages of the first volume consist of a description of the medical organization of the Hospital and then a very interesting commentary of the work (cases of special interest and usually a short description of the policy adopted in management) table by table. The remainder of volume one and the other 2 volumes consist of detailed tables as recommended by the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists.

The Hospital had 253 obstetrical beds available, not all in the parent hospital, for it was (and probably still is) the plan to move patients on the second day after delivery to their own homes or to after-care beds. For patients in their own homes, a domiciliary postnatal nursing service operates and in the year under review made 16,001 visits to 1,565 patients. Concerning the after-care beds, let the report speak for itself.

"*After-care beds:* Every endeavour is made to move the normal delivered mother from the busy hospital atmosphere. Patients who are unsuitable for domiciliary postnatal care for medical, domestic or social reasons are transferred to after-care beds on the second day following delivery where they remain under the care of the hospital staff. Fifty after-care beds are situated three miles from the hospital. Here the wards are situated in a quiet garden setting, in an atmosphere devoid of the usual noise and activity of a hospital. Under these circumstances visiting hours are no problem and additionally mothers are permitted to be visited with certain safeguards as regards infection, in the gardens (but not in the ward) by their other children—a privilege that is highly appreciated. The patients are discharged on the ninth or tenth day following delivery, returned to good health and, usually, fully breast feeding their babies.

"The system of transfer to such a convalescent unit has not only proved a great boon to the patients, but has also resulted in an economy in the use of after-care beds in the main hospital. These latter beds around which there is the greatest concentration of medical and nursing skill are now principally used for sick patients and for patients in the initial two days following delivery . . ."

The total number of births was 7,294, the still birthrate 14 per 1,000 live and still births in booked cases (109·7 in unbooked cases) and the neonatal death rate 6·5 per 1,000 live and still births (69·1 in unbooked cases). Four maternal deaths occurred.

A few figures will suffice to indicate the extremely high standard of work at this Hospital and the satisfactory results obtained. Twenty-two cases of maternal diabetes were treated with 4 infant deaths, but one was previable (pregnancy terminated because of epilepsy and mental deterioration) and one had an absent hemidiaphragm. Twelve cases of eclampsia occurred, none being ante-natal and only one patient had more than 2 fits; only one baby died; the post-partum haemorrhage incidence was 2·5 per cent and that for manual removal of the placenta 4·6 per cent (not 4·6 per 1,000 deliveries as stated in the report); ergometrine 0·5 mg. was given intravenously as soon as possible after the delivery of the baby followed by 0·5 mg. intramuscularly. The Caesarean section rate was 3·4 per cent (the Classical route being 7 times in 240 cases) and the forceps delivery rate 8·5 per cent.

A Paediatric Report is included and also a Report of the Department of Gynaecology. The Obstetric Report would be greatly enhanced by a table of comparative statistics, say for the previous 5, or preferably, 10 years.

THE 10TH ANNUAL REPORT FROM THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, AT ST. LUKE'S HOSPITAL, ANUA, UYO, EASTERN NIGERIA

THE Obstetric Department of this hospital had 50 beds available in 1956, and delivered 729 babies, 515 of the cases being booked. The Caesarean section rate was 4·1 per cent, the forceps rate 5·1 per cent, and the neonatal death rate 2·8 per cent. The report consists of the tables

recommended by the Standard Maternity Hospitals Reports Committee of the Royal College; it includes an introduction to the Maternity Section which states: "This department still competes with the native bush doctor and midwife . . . Diseases rife in this district are malaria, yaws, helminth infestations and gonococcal infections of genito-urinary tract, malnutrition, and nutritional anaemia." Symphysiotomy was performed frequently, 89 cases being recorded; there were 8 cases of vaginal delivery following previous symphysiotomy.

There is a short report about the gynaecological department. Thirty beds were available and 750 patients were admitted. Sterility was a major problem, and a very large number of cases suffer from some form of salpingitis. Many patients had plastic operations on their tubes. Twenty-six vesico-vaginal fistulae were repaired and 441 Gilliam and other suspension operations were carried out. Only 6 cases of ectopic pregnancy occurred, a surprisingly low figure.

The Departments of Obstetrics and Gynaecology are to be complimented upon a successful year's work, and upon a speedy publication of their report, working as they are in conditions very different from those in the British Isles.

THE CLINICAL REPORTS FOR 1956 OF THE MATERNITY HOSPITALS OF THE TEACHING HOSPITALS BOARD OF THE UNIVERSITY OF CAPE TOWN

1. The Peninsula Maternity Hospital.
2. The Mowbray Maternity Hospital.
3. The New Somerset Hospital, Shipley Ward.
4. The St. Monica's Maternity Hospital.

In reviewing the 1955 reports of these hospitals the complaint was made that although it was apparent that there was a difference in the type of case selected for admission for some of these hospitals, no indication was given in the reports about the nature of this variance. As this criticism still holds good no attempt will be made to compare results.

A total of 6,898 patients were delivered, with 8 maternal deaths, 276 stillbirths and 182 neonatal deaths.

THE MEDICAL REPORT OF THE MATERNITY HOSPITAL AT LEEDS FOR 1951

One's first reaction to this report was to disbelieve the date on the cover. However, as 1951 is repeated on several pages, one must assume that the delay in submission for review is due to a good reason. It is a fact that the reports published most promptly come from the more remote parts of the Commonwealth; and fresh news is always more interesting news.

The report states that there was no major change in policy during 1951. A reduction in the number of bookings (from 1,750 to 1,494) was due to rebuilding of the labour ward and out-patient department. The only table of comparative statistics refers to the numbers of babies lost per 1,000 booked deliveries compared with the incidence of Caesarean section in booked cases (8·3 per cent in 1951). To quote the report: "The incidence of Caesarean section continues to rise. The extra operations are being done mainly to save babies; the figures do not demonstrate this effect."

The hospital delivered 1,750 patients; of these 285 were unbooked cases. Four maternal deaths occurred. The stillbirth rate (per 1,000 live births) was 48·7 and the infant deaths (per 1,000 live births) was 27·56.

The report follows the recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists.

THE CLINICAL REPORT OF THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY OF THE GENERAL HOSPITAL, KUALA LUMPUR, MALAYA, FOR 1957

This is the fifth annual report to appear from this hospital and like its predecessors it is published promptly (compare with many from the British Isles!) and is very entertaining to read. It consists of a statistical summary for the year, a useful table of comparative statistics for the years 1953–1957 inclusive, an introduction giving details of the type of patient admitted and the difficulties under which the department works. The bulk of the Report consists of abstracts made from the tables as recommended by the Committee of the Royal College of Obstetricians and Gynaecologists together with comments and information about the treatment given.

During 1957, 6,898 women were delivered (an increase of 499 from 1956). There are 40 antenatal beds and 75 postnatal beds. Patients accepted are those with an abnormality of the present pregnancy or previous pregnancy or confinement, primigravidae and all women in the sixth or subsequent pregnancy. Obviously, there is great pressure put on the beds available; a survey in May, 1957 of 500 consecutive deliveries, showed that 51·2 per cent of patients were discharged within 48 hours of delivery and 87·3 per cent by the 7th day.

Thirty maternal deaths occurred and are described in an appendix. As may be imagined, most of the complications of obstetrics are included; the majority of the cases appear to be due to neglect on the part of the patients in failing to carry out advice.

The Caesarean section rate was 2·03 per cent and the forceps rate 4·03 per cent; the majority of low forceps deliveries were made under pudendal nerve block anaesthesia. Pre-eclampsia in its mild and severe forms occurred more than in 1956, 514 patients being admitted (104 had not attended an antenatal clinic); the incidence was 7·5 per cent of all deliveries. Forty-one cases of eclampsia were treated with 4 maternal deaths (= mortality rate of 9·3 per cent); 27 were emergency admissions. The foetal mortality rate was 42·85 per cent. A mixture of phenothiazine derivatives continues to be used in the treatment of eclampsia and it is stated to be the best form of treatment they have encountered so far.

It is a pleasure to congratulate the department on the excellence of this report.

THE CLINICAL REPORT OF THE CRESSWELL MATERNITY HOSPITAL, DUMFRIES, FOR 1955

THIS report follows the recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists. Whereas this is the 1955 report and the 1953 report has recently been reviewed, the 1954 report has so far not been presented for survey. In 1955 the hospital delivered 1,525 patients, of which 232 were unbooked. One maternal death occurred in an unmarried multipara who denied the possibility of pregnancy; but she was 7 months pregnant and suffering from severe pre-eclampsia, being nearly blind on admission. She died during the induction of anaesthesia for a proposed Caesarean section from collapse due to acute heart failure. Seven cases of eclampsia were treated (all but one were booked cases), in each case by rectal Tribrom Ethanol; the only foetal death occurred in the unbooked case.

An interesting case is described of a woman aged 30, para-3, who at term was admitted because of hypertension and unstable lie of the foetus. Several medical inductions were given and at the 44th week she was surgically induced by artificial rupture of the membranes; after 2 days she complained of right-sided pain and a volvulus was diagnosed in the ileocaecal region and confirmed by laparotomy. She made a good recovery and delivered herself of a live child weighing 8 pounds 3 ounces a few hours after.

CLINICAL REPORT OF THE MATERNITY DEPARTMENT OF GUY'S HOSPITAL, LONDON, FOR 1956

THIS report utilizes the classification tables recommended by the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists, modified to allow convenient contrast between the unselected midwifery practice of a very compact district and a selected group of patients referred because of anticipated difficulty. Of the total of 1,188 patients, delivered during the year 1956, 154 were confined at home, and 251 of those confined in hospital belonged to the selected group of patients referred from outside the hospital district. A useful summary of results since introduction of annual reports in 1928 shows that the numbers in each category have been fairly steady in recent years, and it is particularly interesting to note that in the past 5 years the cases of anticipated difficulty have done better than the unselected district practice in terms of maternal mortality and foetal mortality.

As in 1955, happily there has been no maternal loss; perhaps for this reason there is no account of cases of special interest. Also noteworthy is the absence of foetal loss from Rhesus incompatibility for the third year in succession. Stillbirths and neonatal deaths in 1956 are combined to give an overall foetal mortality of 2·8 per cent; nil, for birth trauma; 1·8 per cent for forceps delivery (incidence 4·8 per cent); 6·5 per cent for Caesarean section (incidence 2·6 per cent); nil, for surgical induction of labour (incidence 4·3 per cent). It is observed that, among the 51 patients induced, the induction–delivery interval exceeded 48 hours for 15 patients and 72 hours for 8 patients. The longest interval was 17 days; a pitocin drip was used once; Caesarean section was required 4 times.

The tables concerned with toxaemia show 3 patients with eclampsia, 2 of these with twins, and a foetal mortality of 20 per cent. Fits occurred post-partum in 2 of these cases. The infant lost was born prematurely, following accidental haemorrhage. Another patient required abdominal hysterotomy for severe pre-eclampsia. The table for Pre-eclampsia, Hypertension and Chronic Nephritis lists a further 96 patients, all but 17 of whom had albuminuria. Calculation shows that this group of toxaemia cases has an incidence of 8·4 per cent of the total deliveries. Some 13 of these patients had reached or passed the 42nd week of pregnancy, without foetal loss. Only one of the 96 patients had a diagnosis of chronic nephritis; the infant weighed 3 pounds 1 ounce and did not survive delivery by section at the 39th week; this was the only neonatal death. The foetal mortality of the group was 6·9 per cent.

While congratulating the hospital on the work recorded and in general on the clarity of the report, it may be useful to note that post-mortem examinations in cases of stillbirth and neonatal death are infrequent, and to suggest that it would be instructive to have a little more information or perhaps some comment with the summarized table on Post-partum Haemorrhage (incidence 7·4 per cent). *J. Duncan Murdoch*

CLINICAL REPORT OF QUEEN CHARLOTTE'S MATERNITY HOSPITAL FOR 1954

IN the preface of this report there is mention of investigations of various antiseptics in the Bernhard Baron Research Laboratory of the hospital and of the adoption of chlorhexidine (Hibitaine) for clinical trial, both as a solution and as an obstetric cream, from the autumn of 1953. It is disappointing and a defect of the standard maternity hospital report, which provides so much detail about patients, that there is no way of discovering by reference to tables of puerperal pyrexia, maternal and foetal mortality, neonatal infections, and comparative statistics, whether the change of antiseptic has been beneficial. Some comment on this point would be interesting in the next report, 1955.

The work of the out-patient (district) delivery service for 469 mothers is neatly and effectively presented in summarized form. Forty-seven patients were primigravidae; there were three twin deliveries; one breech delivery; six forceps deliveries; one labour following

previous Caesarean section. Manual removal of the placenta was required three times; the incidence of post-partum haemorrhage was 8·9 per cent. There were 3 macerated stillbirths and 4 neonatal deaths, 2 of which were due to foetal malformation. Sixteen of the district patients required transfer at some stage to the in-patient hospital service. The rates for stillbirth, 6·4 per thousand, and neonatal deaths, 8·5 per thousand, show the foetal hazards in a group of women presumably regarded as not being obstetrically at risk and give an estimate of the results that can be expected in an expertly selected domiciliary midwifery practice adjacent to a first rate hospital to aid in unforeseen emergency.

The in-patient deliveries were 3,212, all but 16 of which were booked patients, and 2,007 were primigravidae. Rates for maternal mortality were 1·5, stillbirths 22·9 and neonatal deaths 18·4 per thousand.

Both in the preface and in an admirable paediatric report there is valuable comment on the problems of maternal iso-immunization, particularly in reference to guidance from haemoglobin and serum bilirubin levels in the use of exchange transfusions. The last 3 tables present the large experience of the hospital in these problems, giving details of 49 patients including 7 with haemolytic disease due to rhesus antigen D (babies unaffected, Coombs' negative); 7 others due to rhesus antigen other than D; and a large group of 35 patients with haemolytic disease due to rhesus antigen D (affected babies, Coombs' positive). Two of the latter group were very severely affected and were delivered prematurely of macerated infants; 11 patients were managed successfully without exchange transfusion; the remaining 22 cases required transfusion, blood usually being exchanged two or three times and the volume transfused at one exchange being on one occasion as much as 745 ml. in and 775 ml. out. Three of these 22 treated infants failed to survive the neonatal period and one other infant is mentally retarded and spastic. In this group of 33 Coombs' positive cases labour was induced surgically on nine occasions, 5 of which were at or after the 40th week; in no case was delivery obtained before the 37th week.

The tables dealing with stillbirths and neonatal deaths contain much information obtained by post-mortem examination. In this connexion it is notable that malformations (20) accounting for stillbirth appear to be 0·6 per cent of infants delivered, while the overall incidence of abnormality (170) tabulated by systems amount to over 5 per cent of babies born; in only a small proportion of these was the defect of a minor nature not likely to distress the parents.

Ante-partum haemorrhage has been presented in 3 tables. Excluding bleeding from the lower genital tract, there were 4 cases of haemorrhage following version, without foetal loss; there were 5 cases complicating pre-eclamptic toxaemia with stillbirths in 3 of these; and a large group of 41 cases in a separate table described as ante-partum haemorrhage of unknown cause, with 7 stillbirths and 2 neonatal deaths (22 per cent, foetal loss); a maternal death occurred in this group. The table of placenta praevia records 15 patients with 1 stillbirth and 1 neonatal death (13 per cent, foetal loss); all these patients were delivered by Caesarean section.

The descriptions of cases of mortality and of special interest among mothers and babies are most instructive. A word of praise might be permitted also for all those who have helped to compile the long and detailed tables. It is unfortunate that carefully edited and valuable detailed reports like this one by their very nature must appear so long after the events recorded.

J. Duncan Murdoch

SOCIETY FOR THE STUDY OF FERTILITY

ANNUAL CONFERENCE, 1959

on

Thursday, Friday and Saturday, 28th, 29th and 30th May, 1959

at

The Department of Anatomy, Dublin University, Trinity College, Dublin
The Rotunda Hospital, Dublin
The Veterinary College of Ireland, Ballsbridge, Dublin

Honorary Secretary:

A. S. Parkes, *C.B.E.*, F.R.S., National Institute for Medical Research, Mill Hill, London, N.W.7.

Local Secretary:

Raymond G. Cross, M.D., F.R.C.S., M.A.O., M.R.C.O.G., Rotunda Hospital, Dublin.

BOOK REVIEWS

"A Modern Practice of Obstetrics." By D. M. STERN, F.R.C.S., F.R.C.O.G., and C. W. F. BURNETT, F.R.C.S., F.R.C.O.G. 2nd edition. Pp. x+258, with 141 line drawings by Susan M. Robinson. Baillière, Tindall & Cox, London, 1958. Price 45*s*.

THE first edition of this book from the West Middlesex Hospital was welcomed in the December, 1953, volume of this Journal with apt comment on its novel features. This second edition has been partly re-written and new subject-matter includes amniotic embolism, hypofibrinogenaemia (although the association with prolonged retention of a dead foetus is not mentioned), pain in pregnancy and, particularly welcome, a review of the use of hypotensive drugs in obstetrics. There remain, as in all textbooks, views and practices with which some, if not many, obstetricians will disagree. The risks to the foetus of maternal rubella are exaggerated; acute hydramnios is stated to occur only with uniovular twins; frequent small meals are advised in the first stage of labour; and the suggested management of simple prolongation of the third stage is perhaps over-conservative. Certainly the statement that induction of labour for disproportion should only be carried out if facilities for trial labour and Caesarean section are not available is liable to be misinterpreted in theory and misapplied in practice by the inexperienced reader. Nevertheless, the overall impressions left by this book for students and practitioners are of a fresh approach, concise writing, excellence in its account of the toxaemias, and a typography very acceptable to the reader's eye.

"Endocrine Pathology of the Ovary." By JOHN MCLEAN MORRIS, M.D., and ROBERT E. SCULLY, M.D. Pp. 151, with 75 illustrations. Henry Kimpton, 1958. Price £3 3*s*.

THE endocrine pathology of the ovary represents one of the most interesting subjects in gynaecology, and a comprehensive survey of this many-sided field would certainly fill a long-standing gap in the literature. However, the authors of this surprisingly small book only skim the surface and do not penetrate to any extent into the depth of their subject.

The book is very well written and makes good reading for two evenings at the most; it is well illustrated and gives an extensive and exhaustive list of references. The sections on the anatomy and embryology of the gonads are particularly well prepared. However, reading on after this promising start, the student will meet with his first major disappointment, the chapter on Hormone Assays, which confines itself to a mere enumeration of tests in use, without going into details or description of techniques. The classification and discussion of functioning ovarian tumours is conducted on very dogmatic lines, and adds further to the disappointment of the more sophisticated reader.

Despite, or maybe because of the brilliant background of the authors (Yale University School of Medicine, and Harvard Medical School), the expectations aroused by the publication of their book are sadly unfulfilled. Students of gynaecology and endocrinology will certainly find this little volume of interest, but the pathologist and the gynaecological consultant will probably feel that the authors should be encouraged to write a second and much more extensive edition.

"Erythroblastosis Fetalis." By FRED H. ALLEN, JR., M.D., and LOUIS K. DIAMOND, M.D. Foreword by EDITH L. POTTER, M.D., Ph.D. Pp. vii+143, with 8 figures. J. & A. Churchill, London, 1957. Price 30*s*.

THE first impression on picking up this book was that the price was far too high for such a small and unpretentious volume. This first impression was entirely wrong; although the book is small it is tightly packed with useful facts, many of which would be difficult to collect together except from abstruse haematological journals. Indeed, in the end the brevity of the book seemed a major virtue, as it was delightfully easy to read.

There is a good account of the complexities of the Rhesus factor, but obstetricians are now fairly well informed about this, and to them the clear summary of the other rare blood factors will probably be of greater interest. The strange inconstancy of maternal sensitization is discussed, and the importance of the foetal and neonatal response to blood destruction is rightly emphasized, not only as regards bilirubin levels, but also as regards blood regeneration. We find one sentence surprising (p. 43) "Erythroblastosis caused by blood factor A or B is common, comprising approximately two-thirds of all cases . . . Though these cases are much milder on the average than those caused by Rh incompatibility, kernicterus in untreated cases is so frequent that early diagnosis is very important." This is not our experience; is the Boston population different?

The chapters on diagnosis and treatment are essentially practical and are obviously based on wide experience. Full details of the technique of transfusion are included, with a section of valuable hints for technicians.

There are 72 carefully selected references, and a useful glossary of terms used in the text. This is an excellent book, which can be strongly recommended.

"Text Book of Gynecology." By JOHN J. BREWER, B.S., M.D., Ph.D. Second edition. Pp. 742, with 204 illustrations. Baillière, Tindall & Cox, London, 1958. Price £6.

THIS second edition, by a well-known and respected Chicago author, presents a logical approach to diagnosis and treatment through a careful appraisal of presenting symptoms and/or physical signs. Believing that repetition is good teaching, the author divides the book into two parts which are complementary. In the first, well-chosen combinations of symptoms and physical signs are considered during three different eras of life, namely childhood, maturity, and ageing. Each chapter is followed by a thumbnail review of the subject in a form convenient for revision. The special contribution chapter on "Endocrinology" by Dr. DeCosta deserves specific mention for it is comprehensive, authoritative and exceptionally practical in outlook.

Individual pathological entities are dealt with systematically in the second part in order to reinforce what has gone before and incidentally to tie up loose ends that do not fit easily into the first. It is difficult to understand the reason for the division into thirteen chapters when a round dozen would be so convenient. The "extra" chapter on "Sarcoma of the Uterus" is oddly conspicuous.

Following the modern trend, operative details are omitted throughout except in the chapter on carcinoma of the cervix where a just appraisal of modern curative surgical and radiotherapeutic methods is presented. Scant attention, however, is paid to the equally important clinical problem of palliation of the advanced lesion.

Minor errors and omissions melt into insignificance compared with the overall excellence of the book. Above all the approach is exceptionally reasonable and nowhere is this more apparent than the chapter on "Sterility" where the value and limitations of investigation and treatment methods are described succinctly and without bias.

The reader who is in search of scientific truth will find this book a rewarding stimulus and a practical guide to the clinical management of his patients. It is indeed a brave, successful and highly commendable attempt to present a new approach to clinical teaching.

"Lehrbuch der Gynäkologie." By PROFESSOR HEINRICH MARTIUS. 5th edition. Pp. xvi+426, with 456 illustrations. Georg Thieme Verlag, Stuttgart, 1958. Price D.M.49.80.

THE latest edition of Professor Martius's Textbook of Gynaecology is the fifth to appear since it was first published 12 years ago. This, together with the fact that it has been translated into Italian and Spanish, is a measure of its popularity with undergraduate students on the Continent. Its success is no surprise since the author presents systematic gynaecology in a clear, concise and easily readable form. Gynaecological anatomy and physiology and the details of operative technique are not dealt with as Professor Martius has devoted separate books to these subjects.

The author presents his subject by subdividing it according to the underlying pathological anatomy of the affected organs. The first chapter describes functional disorders of the female reproductive tract and discusses the uses and limitations of hormone therapy. There follows a chapter dealing with pain of gynaecological origin. The section dealing with displacements of the uterus seems unbalanced since 15 pages are devoted to retroversion and only 20 pages to the subject of prolapse. Carcinoma of the genital tract is very well presented and this chapter includes an up-to-date evaluation of exfoliative cytology and the significance of pre-invasive carcinoma. The book concludes with useful chapters on gynaecological urology and orthopaedics.

The most striking differences between the author's opinions and those current in this country are noticed in his use of radiotherapy, especially for benign gynaecological conditions. A radium menopause is recommended for functional uterine bleeding and the place of radiotherapy in the treatment of fibroids is also extensively discussed. Subtotal hysterectomy is performed for functional bleeding and uterine fibroids in young nulliparae, when operative interference is necessary. The author's concept of leucoplakia and kraurosis vulvae does not conform with the views at present expressed in the English literature.

The book is well illustrated, mainly by drawings, many of which are coloured. Especially instructive are the illustrations designed as visual aids to the interpretation of physical signs elicited on bimanual examination. But, in spite of the high quality of Miss Droysen's illustrations, it is difficult to understand why Professor Martius has chosen to use drawings rather than photographs of patients, pathological specimens and histological details.

References are omitted but authorities are mentioned by name—naturally the majority are German, but American and English work is also quoted.

The publishers are to be congratulated on the production of this book. The binding, paper, type and illustrations are all of the highest quality.

"Gerichtliche Geburtshilfe." By PROFESSOR H. NAUJOKS. Pp. xii+247. Georg Thieme Verlag, Stuttgart, 1957. Price D.M.27.

PROFESSOR NAUJOKS, the director of the department of obstetrics and gynaecology in the University of Frankfurt, is recognized as a leading expert in legal problems associated with his speciality in Western Germany. His monograph is mainly directed at those who may be called upon to give evidence or who may find themselves involved in legal proceedings connected with obstetrical problems. The author states clearly the underlying principles on which judgments must be formed. He underlines the differences existing between medical and legal opinion, but at the same time by logical thinking and by sifting out irrelevant detail he seeks to unify

medical and legal thought on the fundamental issues. He points the problems and illustrates the principles involved in forming an opinion by numerous quotations from cases in which he was involved. The author's style is personal and in expressing opinions on moral and ethical problems he is unhesitatingly dogmatic. However in this respect his opinions are acceptable and form an admirable code of behaviour which any obstetrician could be proud to follow.

The 12 chapters of the monograph are devoted to the following subjects: the problems of and associated with the definition of neonatal death and stillbirth, therapeutic abortion, criminal abortion, infanticide, trauma in pregnancy, sudden death during pregnancy, labour and the puerperium, paternity, professional silence in obstetrics, consent to operation, mistakes and accidents in practice, malpractice and the obstetrician in court. There is a bibliography at the end of the book arranged according to chapter headings.

Although there are important differences between German and English law this book would be of value to anyone in this country who is called upon to give evidence in court on obstetric problems.

"Operative Obstetrics." By PROFESSOR R. GORDON DOUGLAS and DR. WILLIAM B. STROMME. With Foreword by NICHOLSON J. EASTMAN. Pp. xi+735. Illustrated. Appleton-Century-Crofts Inc., New York, 1957. Price 150s.

THIS volume could be regarded as complementary to Eastman's *Obstetrics* and deals very fully with all the standard obstetrical manœuvres. Any attempt at reviewing a book of seven hundred pages in any detail is an impossible task. All your reviewer can do is to indicate very briefly some points of interest. The early chapters deal with anatomy, pre-operative care, anaesthesia and resuscitation of the newborn. The surgical anatomy and techniques of the Pfannenstiel incision are well described and illustrated. The authors advocate pudendal nerve block on all possible occasions and this method, now so widely practised in British maternity hospitals, is fully discussed and depicted by means of drawings and photographs. It is good to read that direct laryngoscopy is advocated in asphyxia of the newborn. Reference is not made to Donald's work on assisted respiration, however. Abdominal hysterectomy for the termination of pregnancy is fully described but the incision recommended is longitudinal and not the lower transverse incision advocated by many British obstetricians. The New York Lying-in Hospital was early in the field in the method of "pitocin drip" induction of labour and this is authoritatively discussed. Some of the older obstetricians in this country will be delighted that induction by bougie is illustrated and described. Those of more tender years will bemoan the fact that their favourite weapon for performing amniotomy, the Drew-Smythe catheter, obtains no mention at all. The chapter dealing with forceps delivery is a very comprehensive one, and the use of Kjelland's forceps is ably dealt with. Haig Ferguson's forceps receive an honourable mention under the name "Hague-Ferguson". It is sad to have to record that Lövset's manœuvre, so popular a technique for delivering the arms in a breech extraction in Commonwealth hospitals, is not described.

Caesarean section is considered in detail and a transverse incision advocated in the lower segment operation. Caesarean hysterectomy as a method of sterilization is (very wisely) not recommended. The remaining chapters of the book deal with the other common obstetric operations and complications: episiotomy, post-partum haemorrhage, etc. A final chapter is concerned with post-operative complications.

Dr. Gordon Douglas is well known to obstetricians in this country and he and his co-author Dr. Stromme are to be congratulated on producing a splendid volume on operative obstetrics. It is unlikely that their book will displace Moir's *Operative Obstetrics* in this country but then the books are really not in competition, for the volume under review is more in the nature of a fully annotated atlas of obstetric operations than a textbook of operative obstetrics. It can be heartily recommended to all who practise obstetrics. Your reviewer would like to pay tribute to Miss Elizabeth Broedel and her colleagues for the excellent illustrations.

"Die Hormonale Behandlung von Zyklusstörungen." By ROLF KAISER, M.D. With a Preface by PROFESSOR W. BICKENBACH, M.D. Pp. viii+48, with 38 figures and an appendix with 10 tables. Georg Thieme Verlag, Stuttgart, 1958. Price (in cardboard cover) D.M.5.80.

IN this booklet the author aims at providing the gynaecologist and general practitioner with guidance in the use of hormones in gynaecological practice. On the whole this aim is achieved, although some of the problems may appear to have been simplified for the sake of clarity, as in the treatment of dysmenorrhoea; but since the author confines himself to the subject of hormone therapy, this is justified.

Having pointed out that the use of hormones is limited to a number of "functional" disorders, he describes the treatment of the various types of amenorrhoea, anovulatory and abnormal ovulatory cycles, ovulation bleeding, pre-menstrual bleeding, premenstrual syndrome, advancement and postponement of menstruation and a few obstetric conditions. Care is taken to avoid blunderbuss treatment by providing a rational basis as far as present-day knowledge permits. Hormonal treatment is preceded by obtaining a record of the basal temperature and full use is made of vaginal smears for the control of treatment, and of endometrial biopsy, examination of cervical mucus and hormone tests for the study of the response of the endometrium and the ovary.

By making free use of diagrams the author has avoided lengthy accounts of methods of treatment.

As references have been deliberately omitted from the text the reader is unable to study the evaluation by other workers of the various schemes of treatment. The book would therefore not be sufficient for the gynaecological endocrinologist.

Nor-testosterone has evidently been fully accepted as the most useful available preparation for producing progestational effects.

The bibliography at the end of the booklet contains only publications in German. There is a useful appendix giving the names of the numerous commercial preparations on the German market.

The printing is of high standard.

"Abdominal Operations by the Vaginal Route." By PAUL WERNER, M.D., and JULIUS SEDERL, M.D., with a foreword by RICHARD W. TE LINDE, M.D. Pp. 165. 120 plates. Pitman Medical Publishing Co., London, 1958. Price 65*s*.

THE title of this book is its own condemnation. In the preface it is claimed that operations by the vaginal route carry a lower mortality and morbidity than comparable abdominal operations. This may be true for straightforward cases of vaginal hysterectomy, but few will believe it to be true for such procedures as morcellement of large fibromyomata, removal of ovarian cysts or operations for ectopic pregnancy. There is perhaps something to be said for the authors' affirmation that every gynaecologist should know of these techniques, but they admit that extensive surgical experience is necessary before they can be safely employed, and few surgeons would agree that they have any real advantage over the usual methods.

The descriptions and illustrations of the operations are beautifully clear, and the difficulties that may arise are particularly mentioned, with the best methods of overcoming them. In these operations the instruments required and the exact steps to be followed by the assistants are of importance, and these matters are exactly described. The account of vaginal hysterectomy contains many details of great interest. It is curious that the Schauta operation, for which there has been so much enthusiasm in some continental clinics, is not even mentioned; on the other hand such procedures as tubal sterilization by the vaginal route, vaginal operations for ectopic pregnancy, interposition, and vaginal fixation of the uterus are included.

The authors are obviously master surgeons, and the illustrations are drawn from actual operations. No criticism could be made of the form and production of this book, and the translation by Dr. L. M. Szamec is excellent. Yet it can hardly be recommended except for those who wish to satisfy themselves that they have studied every possible technique. As propaganda for the vaginal route it is unconvincing.

"Gynecologic and Obstetric Pathology with Clinical and Endocrine Relations." By EMIL NOVAK, A.B., M.D., D.Sc., F.A.C.S., F.R.C.O.G.(Hon.) and EDMUND NOVAK, A.B., M.D. Fourth edition. Pp. xv+650, with 683 illustrations, 25 in colour. W. R. Saunders Co., Philadelphia and London, 1958. Price 98*s*.

THIS may rightly be regarded as the most authoritative statement in the English language on certain aspects of obstetrical and gynaecological pathology. The last edition was in 1952 so that this, the fourth edition, still has the advantage of Dr. Emil Novak's share in revision before his lamented death early in 1957. There are new chapters on Implantation and Placentation and on Diseases of the Placenta by Professor Robert E. L. Nesbitt and on Exfoliative Cytopathology by Dr. John K. Frost.

The general plan throughout is to preface the discussion of the pathology of each organ—Cervix, Endometrium, Fallopian tube, Ovary, Placenta—by an outline of the normal histology. Whilst the "naked-eye" pathology receives adequate notice the emphasis is on histology. It is in this field that Emil Novak was supreme. In this sphere he holds a place of high honour beside the late Robert Meyer.

In limiting their discussion to the pathology of the female pelvic organs the authors have deliberately excluded large areas of the pathology of obstetrics. Thus the sole references to toxaemias of pregnancy are in the section dealing with placental pathology. There is no reference to pelvic contraction and disproportion. Similarly large areas of gynaecological pathology, e.g., displacements, do not appear. The descriptions are, in short, restricted to "pathology" as this ordinarily applies to a laboratory to which organs are carried for special study especially of a histological nature.

The volume is handsome and the illustrations are of the highest standard.

REVIEW OF CURRENT LITERATURE

CONTENTS

	REF.
ANATOMY	297
PREGNANCY	301
LABOUR	309
LACTATION	311
INFANT	312
GYNAECOLOGY	313
Infections of the Reproductive Organs	329
New Growths of the Reproductive Organs	333
Operations	334

ANATOMY

297. **The Relationship Between Columnar and Squamous Epithelium in the Uterine Cervix During the Life Span of Women.** (Die Beziehungen des Schleimepithels zum Plattenepithels an der Cervix uteri im Lebenslauf der Frau.)

By P. SCHNEPPENHEIM, H. HAMPERL, C. KAUFMANN and G. K. OBER. *Arch. Gynäk.*, **190**, 303–345. 1958. 28 figs. 18 refs.

The paper is based on the histological findings in 853 uteri, 258 of which were collected from post-mortem examinations and 595 from hysterectomies. Extreme care was taken pre-operatively and in the handling and fixing of the specimens to avoid misinterpretation due to artefacts. Pre-operative colpophotography and routine photography before and after fixation were carried out in order to prevent errors in diagnosis through distortion. The following conclusions were reached:

(1) The localization of the squamo-columnar junction showed wide variations and was only rarely found at the external os. The squamous epithelium may end at varying distances from the external os or may reach into the cervical canal as far up or even further than the internal os; the columnar epithelium, on the other hand, may reach down and beyond the whole length of the cervical canal to cover the surface of the portio vaginalis.

(2) There seemed to be a definite relationship between age and ovarian function on one hand and the distribution of the epithelial borders on the other.

(3) In children squamous epithelium was often found on the surface of the portio vaginalis, frequently penetrating into the cervical canal. The cervical glands only rarely reached down as far as the level of the external os, being confined to the cervical canal as a rule.

(4) During the reproductive period the cervical glands frequently reached the portio vaginalis.

(5) After the menopause the cervical glands were again restricted to the cervical canal. The older the woman, the greater the tendency of the squamous epithelium to grow into the cervical canal. The authors believe that the glands retract rather than atrophy.

(6) The findings in parous and nulliparous women were not at variance.

(7) In 75 per cent of the cases colpophotographic findings corresponded well with the histological findings in surgical specimens. The reasons for discrepancies were ascribed to distension of the vault by the speculum or to the presence of large retention cysts whose ducts could not be visualized accurately by colposcopy.

(8) Whereas the squamo-columnar junction in younger women was often the seat of erosions, inflammations and inadequate epidermidization, marked epidermidization was a very common finding in older women.

(9) Erosions and inadequate epidermidization were more frequently found in pregnant than non-pregnant women.

E. Wachtel

298. **Lymph Follicles in the Cervix Uteri.**

By N. J. DEMETRAKOPOULOS and R. R. GREENE. *Surg. Gynec. Obstet.*, **106**, 729–733. June 1958. 6 figs. 6 refs.

This is a study from Chicago of the structure, frequency and distribution of lymph follicles in the cervix. Twenty-nine adult cervices and 12 foetal cervices were examined in addition to 86 multiple biopsy specimens.

Fourteen (48 per cent) of the serially blocked cervices contained lymph follicles. These lay either directly beneath the cervical epithelium or deeper in the stroma of the cervix. Heavy or moderate chronic inflammation was present in more than 3 times as many cervices with lymph follicles as without them. Of 86 multiple biopsy specimens examined, 8 contained lymph follicles and 6 of these 8 were associated with marked chronic inflammation. The lower incidence of lymph follicles in the biopsy specimens is probably due to the fact that often only a small part of the stroma accompanied the epithelium and thus many lymph follicles could have been missed.

No lymph follicles were found in the mucosa of 12 serially sectioned foetal cervices. (All foetuses were at least of 26 weeks gestation.) This observation supports the view that lymph follicles are not congenital structures and are probably evoked by inflammation.

In the presence of heavy chronic inflammation, in addition to lymph follicles, less well circumscribed lymphoreticular islands were present and it seems likely that the function of the 2 structures is the same.

John P. Erskine

299. **The Glandular Structures of the Cervix Uteri.**

By C. F. FLUHMANN. *Surg. Gynec. Obstet.*, **106**, 715–723. June 1958. 9 figs. 7 refs.

This report from San Francisco is based on a study of the cervical mucosa by (*a*) visual inspection of the gross surface markings of the cervical canal; (*b*) examination under a stereoscopic microscope of thick sections of cervix previously cleared in xylol and oil of wintergreen; (*c*) plastic reconstructions of the cervical mucosa prepared from serial microscopic sections. Eighty specimens were available from cases in which total hysterectomy had been performed for various pelvic lesions not primarily involving the cervix.

The author found that the grossly visible folds of the cervical mucosa did not show a regular pattern of arborization as previously described. No consistent arrangement could be determined and the folds were found to run in longitudinal, transverse and oblique directions to form a very irregular arrangement of grooves. The basic structure of the cervical epithelium was not that of a tubular gland originating at the surface, but a cleft or groove with large numbers of fine irregular clefts arising from it. The tubular structures, formerly described as glands descending from the surface, proved to be straight tunnels running parallel to the surface and originating from the depths of the clefts.

In discussing the morphogenesis of the cervical clefts, the author suggests that the clefts do not develop from invagination of the epithelium but by a complicated process of exophytic growth.

John P. Erskine

300. **Microscopical Examination of the Capillaries by Reflected Light During the Menstrual Cycle and the Puerperium.** (Microscopia capillare a luce riflessa in rapporto al cicle mestruale e allo stato puerperale.)

By CARLO LURASCHI. *Ann. Ostet Ginec.*, **78**, 441. May 1957. 21 figs. 189 refs.

In this very long but well illustrated article the author describes changes seen in the capillaries in women during the phases of the menstrual cycle, during pregnancy and during the puerperium. Observations have been made with a reflected light colpo-microscope, and the cervix uteri and the labia minora have been mainly studied.

In the premenstrual phase, 48 hours before menstruation, the capillaries are dilated with stasis in the venous ramus. Excessive permeability of the capillary wall is evident. At 12 hours before the flow, the capillaries are still dilated but with increased permeability, transudated fluid surrounds them. During menstruation the capillaries are dilated and serpiginous; permeability is much increased. Four days after menstruation the capillaries appear normal with no dilatation. At the end of the follicular phase the capillaries are again dilated but with no evidence of transudation or increased permeability.

In early pregnancy the capillaries appear normal except for some slight venous vasodilatation. Stasis and venous dilatation become more evident as pregnancy proceeds. By the last trimester the capillaries are grossly dilated with an abundant surrounding transudate. During labour, small haemorrhages may be seen around groups of capillaries, with some spasm of the capillaries and precapillary vessels.

On the first day of the puerperium, numerous widely dilated capillaries are seen, with intermittent spasm and some increased permeability. By the seventh day a constant dilatation of the capillaries persists with a surrounding zone of oedema. By the fortieth day the appearance is almost normal apart from slight stasis. By the seventieth day, there is nothing to be seen apart from slight spasm and oedema.

Josephine Barnes

PREGNANCY

301. **The Passage of Radio-active Strontium (Sr^{89}) Through the Placenta and Into Milk.** (Sul passaggio dello stronzio radioattivo (Sr 89) attraverso la placenta e il latte—Stuido sperimentale.)

By U. MARINONI and S. AVANSINI. *Ann. Ostet. Ginec.*, **79**, 147. Feb. 1957. 4 refs.

A study of the passage of radioactive strontium (Sr^{89}) through the placenta and into milk has been studied, using guinea-pigs as the test animals.

The first series consisted of 8 foetuses removed from guinea-pigs treated with radioactive strontium at the beginning of pregnancy. Strontium was found in the foetal bones, the highest concentration being in the cranium, with lesser amounts in the humerus, femur, tibia, and fibula. Five foetuses from mothers treated at the end of pregnancy showed the higher concentration in the limb bones with lesser amounts in the cranium. No specific lesions could be found in the placenta, but the isotope was found to be concentrated especially in the syncytial layer and in the Langhans' epithelium.

Radioactive strontium was also injected intramuscularly into seven lactating guinea-pigs. Appreciable amounts of the isotopes were detected in the long bones of the sucklings. It is noted that the bones take up the isotope selectively whether it is given to the pregnant or the lactating animal.

Josephine Barnes

302. **The Permeability of the Amnion to Proteins (Experimental Research with Sero-Albumin Marked with Radio-Iodine).** (Permeabilita amniotica alle proteine (Ricerca sperimentale con siero-albumina marcata con radiojodio).)

By G. B. CANDIANI. *Ann. Ostet. Ginec.*, **79**, 209. Mar. 1957. 4 figs. 6 refs.

The permeability of the amnion to proteins has been studied in the female rat by injected serum albumin marked with radio-iodine. By paper chromatography and autoradiography it has been shown that the radioactive iodine remains linked to protein.

It is found that the content of radioactive iodine in the mother's serum falls rapidly after 6 hours but a constant level is maintained from 21 to 42 hours.

In the foetus there is a peak of radioactivity in the serum at 6 hours, None is detected in 21 hours, while there is a small amount at 42 hours. The passage of radio-iodine at six hours indicates a mechanism of equilibrium between the maternal and foetal circulations. The very low foetal concentration at 21 hours is taken to represent a return of albumin to the maternal circulation. The rise at the 42nd hour is comparatively slight compared with that at the 6th hour. This is regarded as a secondary effect and probably due to direct participation by the foetus. There may be some renal secretion.

Josephine Barnes

303. **The Mode of Action of Prostigmin in Heartburn of Pregnancy.**

By C. L. SULLIVAN. *West. J. Surg. Obstet. Gynec.*, **66**, 161–162. May–June 1958. 9 refs.

By using a prostigmin analogue "Mestinon" which has no "muscarinic effect", the author has shown that heartburn is due to a distorted and lagging gastro-intestinal tract and that relief is obtained by inhibiting cholinesterase.

D. C. A. Bevis

304. **Habitual Abortion.** (L'avortement habituel.)

By V. B. GREEN-ARMYTAGE. *Gynéc. prat.*, **9**, 7–12. 1958. 7 figs. 4 refs.

The author believes that habitual abortion is very often due to a weakness, congenital or acquired, of the internal os. He considers that it should be suspected in:

(1) Patients who have undergone dilatation of the os or amputation of the cervix.

(2) Patients who have had a rapid spontaneous, or forceps delivery of a large infant.

(3) Those who have already had one, or several rapid, complete, pain-free abortions.

When such patients are seen in the non-pregnant state, the diagnosis may be confirmed by the ease with which a Hegar dilator of size 4 or 5 may be passed through the entire length of the cervical canal, or by a radiological technique utilizing an opaque medium in a balloon to outline the canal. During pregnancy one finds a relaxed external os which admits the index finger along almost the whole length of the canal.

The operation described by Shirodkar in 1954 utilizes fascia lata to narrow down the cervical canal. Although this operation is admirable in many ways it is painful, necessitates prolonged hospitalization and has a failure rate of twenty per cent.

The author claims that his modification of the operation has resulted in a much more simple technique, that it is more efficacious in both the pregnant and non-pregnant states, and that when correctly executed it should give a hundred per cent success.

The operation consists of a technique by which the internal os is surrounded with a strand of 7 or 8 gauge nylon or kangaroo tendon. The technique is well described in the text and equally well shown in the illustrations. The tension of the suture must be adjusted in the non-pregnant patient until it is just sufficient to hold a No. 4 Hegar dilator in the canal. When the patient is pregnant, the exact tension is a matter for personal appreciation, but great tension is not required.

Geoffrey Dixon

305. **A Comparison of the Hematologic Response Following the Routine Prenatal Administration of Intramuscular and Oral Iron.**

By J. A. PRITCHARD and C. F. HUNT. *Surg. Gynec. Obstet.*, **106**, 516–518. May 1958. 2 tables. 2 refs.

This is a study from Dallas, Texas, of the value of the routine administration of iron either orally or intramuscularly to pregnant patients whose diets were thought to be inadequate.

Patients late in the second trimester of pregnancy were assigned at random to one of three groups. One group of 49 subjects was given an iron-free placebo, another group of 74 was instructed to take tabs. ferrous gluconate 0·3 g. 1 t.d.s. throughout pregnancy, while the third group of 49 received 100 mg. of iron intramuscularly as iron dextran. The average interval between the initial and final haemo-

globin measurements in all three groups was approximately 11 weeks. The average increase in the concentration of haemoglobin in each group was 0·3 g., 1·4 g. and 1·6 g. respectively.

A detailed analysis is presented of the patients in each group according to their haemoglobin concentrations at the beginning and end of the study. In the dosage prescribed no advantage was demonstrated from administering iron intramuscularly over simply giving it orally. The authors conclude that the administration of iron to pregnant patients receiving poor diets produces an appreciable improvement in haemoglobin concentration, but for routine use iron by the intramuscular route is not significantly superior to ferrous gluconate taken orally.

John P. Erskine

306. **Porphyria Complicated by Pregnancy.**

By D. R. NEILSON and R. P. NEILSON. *West. J. Surg. Obstet. Gynec.*, **66**, 133–149. May–June 1958. 58 refs. 5 tables.

The authors review the literature and add 3 new cases to the 37 already reported. All but 5 suffered from the intermittent form of the disease and 95 per cent showed an exacerbation during pregnancy. There were 17 maternal deaths, a death rate of 58 per cent in primigravidae and 42 per cent in the whole series. Twenty-five pregnancies ended in abortion 10 of these being therapeutic. There is little that can be done to treat these patients but care must be taken to avoid toxic agents such as barbiturates, sulphonamides and alcohol.

[This is a good review of the subject.]

D. C. A. Bevis

307. **The Carpal Tunnel Syndrome in Pregnancy (A Contribution to the Aetiology of Acroparaesthesiae in Pregnancy).** (Über das Syndrom des Canalis carpi in der Gravidität (Beitrag zur Ätiopathogenese der Schwangerschaftsakroparästhesien).)

By K. KRIZ. *Zbl. Gynäk.*, **80**, 597–608. Apr. 12, 1958. 21 refs.

The clinical picture of acroparaesthesiae in pregnancy is described. The patient awakes in the early morning with a feeling of "pins and needles" in the fingers of one or both hands. The fingers feel swollen, numb and stiff and the first movements may be clumsy. The symptoms usually extend over the cutaneous distribution of the median nerve in the hand. The condition may be precipitated by manual work involving differential finger movements.

The author believes that there is an increase in the interstitial fluid in the connective tissue of the carpal tunnel, causing a relative stenosis and compression of the median nerve, particularly in the last trimester of pregnancy. The local swelling within the carpal tunnel forms part of the generalized water retention. This is attributed to the salt-retaining action of aldosterone.

The author distinguishes two degrees of local changes: (1) A transient functional block of nerve fibres resulting typically in nocturnal paraesthesiae. This form is found in pregnancy and at the time of the climacteric. (2) In the more severe form the paraesthesiae acquire the picture of causalgia. This type was not met with in pregnancy.

In a study of 400 pregnant women, acroparaesthesiae were observed in 12 (3 per cent). These women had gained an excessive amount of weight. In 10 of them the symptoms were bilateral.

Clinical evidence that the paraesthesiae were due to irritation of the median nerve was obtained by digital compression of the nerve just above the flexor retinaculum; by extreme passive extension of both hands; by maximal active flexion of the hands; and by means of a tourniquet with the pressure in the cuff raised above the systolic blood pressure. The last test proved to be the most reliable, being positive in 11 of the 12 patients. It was equally satisfactory in 21 women of climacteric age. Other causes of paraesthesiae have to be kept in mind such as those of Jacksonian type, degenerative diseases of the spinal cord, compression by spinal tumour, disc protrusion, root-sleeve fibrosis, scalenus syndrome, cervical rib, various types of neuritis, vitamin B deficiency, tetany and coronary insufficiency.

Bruce Eton

308. **The Aetiology of Extra-Uterine Pregnancy.** (De l'étiologie des grossesses extra-utérines.)

By J. G. ASHERMAN. *Gynéc. Obstét.*, **56**, 462–466. 1957. 3 refs.

The accepted aetiology of extra-uterine pregnancy requires reconsideration. Some cases admittedly follow salpingitis, but infection is not evident in the majority of cases. Apart from gonococcal or tuberculous infection some cases may follow instrumentation of the uterus.

The writer draws attention to the fact that infertility may not only follow but also precede the extra-uterine pregnancy. In the present series of 325 cases 16·6 per cent sought advice for infertility before the ectopic pregnancy occurred.

The relationship between extra-uterine pregnancy and miscarriage is interesting. In the writer's series 56 per cent of the women had been curetted prior to the extra-uterine pregnancy, to procure abortion in two-thirds of the cases and in one-third for spontaneous miscarriages. (A publication from the University of Leningrad in 1953, based on 16 years experience of legalized abortion, stated that 40 per cent of their cases of ectopic pregnancy gave a history of previous curettage for termination of pregnancy.)

In this series of 325 cases 21 (6·5 per cent) had a second extra-uterine pregnancy.

The writer suggests that psychological trauma caused by criminal abortion or involuntary miscarriage may affect the endocrine system and be responsible for tubal spasm, causing not only infertility but extra-uterine pregnancy.

D. Maxwell

LABOUR

309. Surgical Induction for Suspected Placental Insufficiency.

By I. Cope and M. G. Pearson. *Brit. med. J.*, **1**, 1211–1213. May 24, 1958. 2 figs. 5 refs.

In recent years it has been the policy at Hammersmith Hospital to induce labour in all cases in which it was feared that continuation of pregnancy might endanger the life of the foetus (e.g., even mild hypertension and pre-eclampsia—postmaturity—cases with a history of bleeding during pregnancy). This resulted in a marked increase in the number of surgical inductions—the rate rising from 2·1 to 14·6 per cent during the years 1951–56.

This policy has not however effected any significant reduction in the overall foetal mortality during the period under review and the conclusion is that, until the placental reserve can be measured, large numbers of women with adequate placental function will be induced to save a few infants from placental insufficiency.

In view of the high foetal mortality (25 per cent) reported when the latent period after induction exceeds 72 hours, Caesarean section was carried out when labour was not established within this time and the Caesarean section rate after induction was 14·5 per cent as compared with the overall rate of 5·4 per cent. The overall rate was not increased however.

The incidence of puerperal pyrexia in induced cases was 9·1 per cent against the overall rate of 5·3 per cent. This was attributed entirely to the increased incidence of Caesarean section. *R. W. Grayburn*

310. Twins: Collision, Impaction, Compaction, and Interlocking.

By E. D. Nissen. *Obstet. Gynec.*, **11**, 514–526. May 1958. 9 figs. 4 tables. 69 refs.

A collective review and analysis of the literature on the entanglements of twin foetuses during labour was undertaken as the result of which 69 cases, including one of the author's, have been classified. Forty-five of the cases presented as breech-vertex, 17 as vertex-vertex, 5 as vertex-transverse, and 2 as breech-breech.

There was no maternal mortality nor uterine rupture. Of the 138 infants delivered, only 78 survived. Embryotomy in one form or another accounted for 28 losses. The overall perinatal mortality was 43 per cent (72 per cent the first baby and 27 per cent the second baby).

The youthful primigravida with uterine hypertonicity, premature rupture of the second sac, or oligohydramnios, has been indicted as a prime suspect.

Although the author gives some useful hints on delivery, he points out that each case is an individual problem and no one has had enough successful cases upon which to base definite rules. *J. G. Dumoulin*

LACTATION

311. Mammary Engorgement Treated with Oxytocin. (L'ossitocino nel trattamento dell'ingorgo mammario.)

By S. De Luca. *Minerva ginec., Torino*, **10**, Apr.15, 1958. 1 table. 47 refs.

This is a re-statement of the development and functioning of the mammary glands under hormonal influences. Briefly, the duct structure proliferates during pregnancy under oestrogenic influence, and the gland acini and alveoli under progesterone. After separation of the placenta, the anterior pituitary secretes prolactin which causes secretion of milk but not its onward passage which is procured by the action of oxytocin liberated from the posterior lobe as the result of the neurohormonal stimulus of suckling. This "lets down" the milk by activating the contractile cells surrounding the acini and ducts. This last step is not always obtained, being much dependent on psychological influences, and if ineffective or delayed, engorgement of the breasts results.

[This is strictly comparable with what often occurs in cows which under disturbing conditions may refuse to "let down" their milk.]

One hundred and fifty women with engorged but not inflamed breasts in early puerperium were treated with an injection of 6 units of oxytocin (pitocin), usually with hyaluronidase, a few minutes before the child was put to the breast. About half of them needed a second dose a few hours later. All experienced relief, usually rapid, dramatic and complete. *W. C. Spackman*

INFANT

312. A Study of the "Sexual Chromatin" in the Cells of the Liquor Amnii in the Prenatal Diagnosis of Sex. (Studio della "cromatina sessuale" nelle cellule del liquido amniotico per la diagnosi prenatale di sesso.)

By C. Pasquinucci. *Ann. Ostet. Ginec.*, **79**, 152. Feb. 1957. 2 figs. 29 refs.

It is possible to diagnose the sex of the unborn child by examination of the cells in the liquor amnii.

In the present study, 30 women have been included, 26 at term and the others from the sixth, seventh and eighth months of pregnancy. Liquor amnii has been obtained either during premature labour or by puncture of the amniotic sac by the vaginal route. Five to ten ml. of liquor are centrifuged, the liquor is decanted and a smear is made from the sediment. This is fixed in Carnoy's solution and then stained. The cells are examined with an oil emersion lens to give a magnification of 900. The presence of "sexual chromatin" is diagnostic of female sex, while its absence denotes male sex.

A practical use of this method for prenatal diagnosis of sex would involve abdominal puncture of the amniotic sac. The author considers this to be too dangerous for routine use. *Josephine Barnes*

GYNAECOLOGY

313. **Statistics of Thrombo-Embolic Conditions in Gynaecology and Obstetrics.** (Statistik der Thrombo-embolie in Gynäkologie und Geburtshilfe.)

By H. STAMM and H. HERTIG. *Zbl. Gynäk.*, **80**, 628–657. Apr. 19, 1958. 12 figs. 19 tables. 135 refs.

After a review of the aggregate statistics from published series of Europe, the United States and Japan, the authors analyze the incidence of thrombo-embolic conditions occurring amongst 27,391 patients treated in the gynaecological department of the University of Basle between 1943 and 1956.

The incidence of superficial thrombo-phlebitis amongst these patients was 3 per cent; of slight thrombo-phlebitis of the deep leg veins 1 per cent; of more marked thrombo-phlebitis of the deep veins 1 per cent; of pulmonary embolism 0·75 per cent; of fatal pulmonary embolism 0·01 per cent. There was a drop in the incidence of thrombotic conditions during the two World Wars, each followed by a rise.

The fulminant type of fatal pulmonary embolism is more common in gynaecological than in obstetric patients, possibly because the average age of the latter is lower. In 50 per cent of fatal embolisms there were prodromal signs. If these had been taken as an indication for prompt and efficient treatment, the subsequent fatal embolism might have been prevented. The other 50 per cent are regarded as an unavoidable minimum mortality. The following predictable, and therefore avoidable, factors are held responsible for those deaths which could have been prevented: inconsistent conservative management (i.e., without the use of anti-coagulants); premature discontinuation of conservative treatment; inadequate anti-coagulant dosage; too early termination of anti-coagulant treatment; and death due to haemorrhage attributed to anti-coagulants (1 case).

The Basle routine for patients suffering from thrombosis or non-fatal embolism includes immobilization for at least three weeks after temperature and pulse have returned to normal. The authors recommend that in future anti-coagulants, if used, should be given for at least three weeks with a daily dosage of 40,000 units of heparin or with an amount of "Coumarin" so as to bring about a Quick-value of 20 per cent.

Bruce Eton

314. **Urinary Excretion of Mucoproteins During the Menstrual Cycle.** (L'eliminazione urinaria delle mucoproteine durante il ciclo mestruale.)

By A. BRAGA. *Ann. Ostet. Ginec.*, **79**, 122. Feb. 1957. 1 fig. 33 refs.

The excretion of mucoprotein in the urine has been estimated in six regularly menstruating women aged between 18 and 20. It was found to follow a cyclical pattern with an increase between the 7th and 12th day of the cycle, a fall between the 12th and 14th day and a second increase from the 15th to the 17th day.

It was concluded that at least part of the excretion is related to the production and excretion of gonadotrophic hormones.

Josephine Barnes

315. **Urinary Elimination of Muco-protein Reducing Substances During the Menstrual Cycle.** (Eliminazione orinaria di sostanze riducenti mucoproteiche durante il ciclo mestruale.)

By A. BRAGA. *Ann. Ostet. Ginec.*, **79**, 203. Mar. 1957. 3 figs. 11 refs.

The daily output of mucoprotein reducing substances has been studied in the urine of regularly menstruating women.

A distinct peak is found during the pre-ovulatory phase, although the author does not think that the results are sufficiently reliable statistically for the method to be used for the measurement of the output of gonadotrophins during the phases of the menstrual cycle.

Josephine Barnes

316. **Dysmenorrhea in High School and College Girls. Relationship to Sports Participation.**

By L. J. GOLOB, W. R. LANG and M. MENDUKE. *West. J. Surg. Obstet. Gynec.*, **66**, 163–165. May–June 1958. 8 refs.

A study of 448 pupils in schools in Philadelphia is presented. These girls were between their early teens and early twenties, two-thirds of them having either no pain or mild pain at their menses. Practically all the girls who were free of pain took part in active sports and it is debatable whether this is the cause or effect of their freedom from symptoms; it is evident however that planned exercise can prevent and alleviate discomfort.

D. C. A. Bevis

317. **Metrorrhagia Due to Failure to Ovulate.** (Les métrorragies par ovulation manquée.)

By C. ROMAN. *Gynéc. prat.*, **9**, 31–37. 1958.

Irregular uterine bleeding associated with failure to ovulate at the time of puberty and at the time of the menopause is a well-known phenomenon. In adult life such failure of ovulation may frequently result in the delay of onset of a period until the time of the subsequent ovulation or of the next expected period.

The author describes a clinical picture which he differentiates from these phenomena. The typical patient he describes is a young woman whose periods have previously been perfectly regular. She begins to bleed fairly heavily at about the fourteenth day of the cycle, that is to say the time when ovulation should have occurred. Her bleeding will continue for two weeks and stop at the time when the next period is due. There are no associated symptoms except that the onset of bleeding may be heralded by moderately severe abdominal pain. Examination occasionally reveals an enlarged ovary, but

this finding is by no means invariable. Endometrial biopsy shows only proliferative activity of the endometrium.

The question of the pathological basis of this condition is discussed and the treatment recommended is a combination of oestrogen and progesterone. No dosage is suggested but large doses are better avoided. This therapy is aimed at reducing rather than arresting the bleeding which will cease spontaneously at the time of the commencement of the next cycle.

The author does not recommend curettage and indeed it is difficult to see why any treatment is required unless the bleeding is heavy. It is maintained that the succeeding cycle will be perfectly normal.

Short case histories of 15 such patients are presented and although there are numerous references in the text to other authorities, no list of references is given.

Geoffrey Dixon

318. **Leucorrhoea in the Young Girl.** (Les leucorrhées de la petite fille.)

By P. MORIN, D. SERSIRON and G. PLANTUREUX. *Gynéc. Obstét.*, **56**, 450–461. 1957. 4 refs.

The writers have investigated 100 young girls who complained of leucorrhoea. The cause was found to be vulval rather than vaginal in 25 per cent of the cases. Although the problem is rarely serious it is also rarely straight-forward, and many causes were found:

Vulvovaginitis:		
Non-specific	47	
Fungal	6	
Gonococcal	4	
Trichomonal	2	
Foreign body	2	
	—	61
Exocervicitis		5
Vulvitis without vaginitis:		
Non-specific	21	
Oxyuris	3	
	—	24
Congenital malformation ..		1
Adolescent physiological desquamation		7
False cases		2
		100

Treatment must be specific when possible, but in many cases sublingual ethinyl oestradiol combined with local antibiotics proved most effective. The local antibiotics used were a liquid form of chloramphenicol, penicillin, streptomycin or terramycin, and occasionally chloramphenicol or terramycin were given by mouth.

As mammary congestion or uterine bleeding may follow the use of oestrogens the mothers of the girls were always warned of these possibilities.

D. Maxwell

319. **Pharmacology and Clinical Use of Ethinyl-Nor-Testosterone (ENT).** (Pharmakologie und klinische Anwendung des Äthinyl-Nor-Testosteron.)

By H.-J. STAEMMLER and C. LAURITZEN. *Zbl. Gynäk.*, **80**, 754–758. May 10, 1958. 20 refs.

The authors review the pharmacological action of ethinyl-nor-testosterone (ENT) and the indications for its use in clinical gynaecological practice. The action of this drug on the endometrium, vaginal smear and cervical mucus resembles that produced by administration of progesterone. It differs from ethyl and methyl-esters by the absence of anabolic and androgenic effects.

Menstruation can be postponed by means of ENT and when treatment is discontinued, withdrawal bleeding follows regularly 1–2 days later. ENT has an anti-oestrogenic action.

The inhibitory action on the hypophysis was demonstrated by the suppression of lactation in 60 patients and by the control of menopausal symptoms in 30 women.

ENT raises the basal temperature in the same way as progesterone. Judged by the effects on body temperature and on menopausal symptoms, the action of ENT begins after 6 hours and lasts about 48 hours.

Clinically ENT has been found to be effective in the following conditions: primary and secondary amenorrhoea of extra-uterine origin; premenstrual syndrome; menstrual irregularities due to corpus luteum deficiency; bleeding preceding the onset of the proper period; functional menorrhagia (haemostatic action); postponement of menstruation; menopausal symptoms; suppression of lactation.

Bruce Eton

320. **An Orally Active Progestative Agent.** (Il metilestrenolone: nuovo progestinico attivo per via orale.)

By C. ANDREOLI. *Minerva ginec., Torino*, **10**, 203–208. Mar. 15, 1958. 10 figs. 18 refs.

This is one of the new synthetic "nor" products, active orally, with the formula 17-alpha-methyl-19-nortestosterone. In a dosage of 5 mg. twice daily it is used in cases of metropathia haemorrhagica to stop the bleeding, and in similar or smaller dosage to produce other progestational effects. Its activity was confirmed not only by prompt relief of the clinical symptoms but by abolition of the fern-leaf crystallization test (which is given equally well by cervical mucus, saliva and nasal secretion), by vaginal cytology, and a rise in basal temperature with secretory transformation of the endometrium.

W. C. Spackman

321. **Comparison of Ovarian and Endometrial Morphology Spanning the Menopause.**

By B. BIGELOW. *Obstet. Gynec.*, **11**, 487–513. May 1958. 23 figs. 7 tables. 50 refs.

The endometrial and ovarian morphology was studied by the author in 300 patients from whom uterus and

adnexae were removed around the time of the menopause. There was evidence that functional relationships between endometrium and ovary persist after the menopause. Hyperplasia and anaplasia or carcinoma *in situ* reached peak incidence 4 to 9 years post-menopausally. The incidence of true invasive carcinoma rose progressively to a peak 10 or more years after the menopause.

With the occurrence of the menopause, and thereafter, the ovaries showed loss of cystic follicular derivatives and increasing alterations of the cortical stroma, including diffuse hyperplasia, cortical thecomatosis, and cortical granulomata. Cortical stromal fibrosis had no rising incidence parallel to that of stromal hyperplasia.

In the premenopausal group significant correlation was found between the presence of luteinized cystic follicular derivatives in the ovaries and abnormal endometrial activity. This was not the case in the menopausal and postmenopausal groups.

J. G. Dumoulin

322. **Urinary Disorders of the Menopause.** (Les troubles urinaires de la ménopause.)

By J. E. Marcel. *Gynéc. prat.*, **9**, 39–48. 1958. 24 refs.

A distinction is made between disorders of the menopause, that is those directly due to the withdrawal of ovarian hormones and the cessation of periods, and disorders at the time of the menopause; the latter are associated with the age of the patient rather than with her endocrine state.

The author admits that his ideas on the effects of the hormonal disturbance of the menopause on the kidneys are not clear cut. He feels that any direct action is unlikely but that hypertension at the time of the menopause may be due to alterations in the balance of the adrenal hormones and that this hypertension may secondarily affect the renal function.

The ureter, he suggests, may well be affected by the withdrawal of ovarian hormones and, in contrast to the well-known result of pregnancy on the ureter, he postulates increased ureteric peristalsis at the time of the menopause and thinks this may be the cause of the nocturia so frequently observed.

The bladder is by far the most important source of urinary disorders at the menopause and indeed the author describes it as, "a veritable endocrine receptor organ", comparable to the uterus and vagina. He uses the term, "cystopathy" to describe these conditions in which the bladder is affected by hormonal imbalance to differentiate them from "cystitis" which is associated with infection. He objects to the term "cystalgia" on the grounds that pain is not the prominent symptom of the disorders in which he is dealing.

The symptoms of this condition are urgency, frequency and dysuria. This latter often takes the form of a burning sensation in the vulva and may be associated with dyspareunia. On examination, little is to be found except occasionally a small degree of prolapse of the urethral mucous membrane, slight urethral tenderness and, "a tendency to kraurosis". The urine is sterile and cystoscopy and urethrography normal. Bladder capacity is unaltered. The uterine cervix may show oedema. The syndrome is capable of variation depending on the time at which it appears relative to the cessation of menstruation.

Treatment is by oestrogens and/or androgens. These are usually given systemically, but good results have been obtained by the instillation into the bladder of a solution containing oestrodiol 2 mg., progesterone 5 mg. and testosterone 10 mg., made up in 10 ml. of propylene glycol.

[Whilst it is not easy to accept all the views and conclusions put forward in this article, a subject that is given scant reference in most British textbooks is presented with great care and thought and perusal of the article is therefore to be recommended.]

Geoffrey Dixon

323. **Clinical Determination of Tubal Patency By Means of the Phenolsulphonephthalein Test.** (Controllo clinico della pervieta tubarica attraverso il "test FSF" (Fenolsulfonftaleina).)

By C. Luraschi. *Ann. Ostet. Ginec.*, **79**, 339. Mar. 1957. 10 refs.

The phenolsulphonephthalein test for tubal patency was first described by Speck (*Amer. J. Obstet. Gynec.*, 1948, **55**, 1048). If phenolsulphonephthalein is introduced into the uterus, it passes through the tubes and if they are patent it is rapidly absorbed from the peritoneal cavity. Its presence in the urine can be demonstrated within half an hour. This was proved by experiments on rabbits.

The author has used this test on 27 patients aged between 19 and 37; each case has been controlled with insufflation, and when this was negative with hysterosalpingography.

The test is carried out as follows: The bladder is emptied and the vagina and cervix disinfected. A cannula is introduced into the uterus and through this is injected 20 ml. of a slightly alkaline isotonic solution of 0·06 per cent phenolsulphonephthalein. The patient is given 250 ml. of water to drink to facilitate diuresis and after allowing 10 minutes for the liquid to pass through the tubes into the peritoneum, the cannula is withdrawn and a tampon placed in the vagina. After waiting a further 20 minutes the bladder is catheterized and the urine is tested against a solution of 10 per cent sodium hydroxide. If this becomes pink or red, the tubes are considered patent; if there is no colouration, they are considered to be closed.

In the present series the test was positive, indicating tubal patency, in 19. In 15 of these tubal patency was confirmed by insufflation; in the remaining 4 in which insufflation was negative, three were found to have the tubes blocked by hysterosalpingography, while in the remaining case, the tubes were patent but with a delayed passage of the radio-opaque medium.

In the 8 cases where the phenolsulphonephthalein test was negative, gas insufflation showed tubal patency in 3,

while the rest were impervious. The total error over the 27 cases was 6 cases of false negatives or false positives, i.e., a 22 per cent error. This error is outweighed by the simplicity and harmlessness of the test which can be simply performed in the consulting room.

[This test for tubal patency seems at first reading to be simple, harmless and potentially useful. The diagnosis of tubal patency is always difficult by any method. An error of 22 per cent seems rather high, but the method would appear to deserve further study.]

Josephine Barnes

324. **The Problem of the Hermaphrodite with Rudimentary and Hypoplastic Gonads.** (Zur Problematik der Zwitter mit rudimentären und hochgradig hypoplastischen Gonaden.)

By E. PHILIPP and H. H. STANGE. *Geburtsh. u. Frauenheilk.*, **18**, 703–723. May 1958. 36 figs. 26 refs.

Five cases from the gynaecological clinic of the University of Kiel, of gonadal dysgenesis in association with intersexual external genitalia are described in detail. Laboratory investigations and the macroscopical and microscopical structure of the gonads (which were removed in every case) are also described. Each case report is illustrated by excellent photographs of the patient, the external genitalia, the operative findings and the histology of the gonads.

Two of the patients were examples of Turner's syndrome, 2 were true hermaphrodites and 1 was a male pseudo-hermaphrodite. From their study of these cases the authors conclude that intersex associated with hypoplasia of the gonads does not constitute a single syndrome, but includes cases of different types. They were unable to draw any conclusions concerning the aetiology or the pathogenesis of the conditions described. They believe that intersex is determined by genetic factors or by genetic factors combined with hormonal influences.

Peter J. Huntingford

325. **The Clinical Aspects of 20 Cases of Intra-Uterine Adhesions.** (Considérations cliniques sur 20 cas de synéchies utérines.)

By P. SIRBU, A. COMAN and E. VEXLER. *Gynéc. Obstét.*, **56**, 521–528. 1957. 6 figs.

Twenty cases of intra-uterine adhesions are described. The most frequent aetiological factors were curettage and infection. The highest incidence was reported following this procedure for retained products, which seems to prove that besides the traumatic and infective factors, the puerperal state of the uterus plays an important part.

Intra-uterine adhesions may cause sterility and habitual miscarriage, as well as hypomenorrhoea, oligomenorrhoea and amenorrhoea. Cervico-isthmic adhesions can often be diagnosed with a uterine sound, but hysterosalpingography is essential in all cases.

As regards treatment, if intra-uterine adhesions have been present for several years, exploration by hysterotomy is advised. In other cases division through the cervical canal is recommended in the first instance.

In 13 out of 20 cases studied the writers brought about unquestionable improvement in menstrual function and 3 cases went to term with 3 living children.

D. Maxwell

326. **Uterus Unicornis.** (Utérus unicorne.)

By A. GRANJON and M. DUBOST. *Gynéc. Obstét.*, **56**, 499–516. 1957. 10 figs. 10 refs.

This rare condition is due to failure of development of one of the canals of Müller and is unlike the more common malformations due to failure of fusion of the two canals. It is not infrequently accompanied by other deficiencies such as congenital absence of one kidney, spina bifida occulta, sacro-iliac abnormalities and aberrations of the anal canal.

The physical signs may be difficult to assess and diagnosis may rest on these points: (1) A small eccentric cervix. (2) The absence of one lateral fornix. (3) Deviation of the body of the uterus to one side, with elongation. (4) No ovary may be felt on the side from which the uterus is absent. (5) Hysterosalpingography shows the lateral situation of the uterus, the oblique tulip-shaped uterine cavity, and the lack of one tube.

Abortion and premature labour are not more common than in normal uteri. On the other hand, malpresentations, particularly oblique breech presentations, are the rule. Abnormal uterine action may occur. No treatment is required in labour, except that Caesarean section is occasionally needed if there are other abnormalities of the vagina or anus. If section is required a longitudinal incision is recommended.

Details of four cases are given. Two required Caesarean section, one for unsatisfactory uterine action, and the other because of an associated congenital abnormality of the anus which had been successfully operated upon at the age of 10 months.

D. Maxwell

327. **Haemolytic Anaemia in Association with Dermoid Cysts.** (Die hämolytische Anämie als Begleiterkrankung bei Dermoidzysten.)

By W. MÜLLER, H. SCHUBOTHE and R. ELERT. *Geburtsh. u. Frauenheilk.*, **18**, 723–734. May 1958. 3 figs. 1 table. 15 refs.

The authors describe a case from the University of Freiburg. A 44-year-old woman complaining of jaundice was found to be suffering from a haemolytic anaemia. Following exhaustive investigations the only aetiological factor found to account for the active haemolytic process was the presence of incomplete warm auto-antibodies in the patient's serum. The anaemia was resistant to prolonged treatment with cortisone and A.C.T.H. Splenectomy was performed also without any improvement in the patient's condition. Repeated blood transfusions were necessary to keep the patient alive. Eighteen months after diagnosis and 6 months after splenectomy,

total hysterectomy and bilateral salpingo-oöphorectomy were performed to remove a dermoid cyst of the left ovary, the right ovary, which contained small endometrial cysts, and the uterus, which was enlarged by multiple, small, intra-mural fibroids. Within 14 days after operation the haemolytic process had ceased and 5 months later the blood picture was completely normal. Two years after operation the patient remained well.

The authors review 7 similar cases which have been reported by other workers. They discuss the pathogenesis of the anaemia. They believe that the haemolytic process was directly associated with the presence of the dermoid cyst. The production of antibodies against the patient's own red cells being stimulated by antigenic substances produced within the dermoid cyst from its protein and lipoid content.

Peter J. Huntingford

328. **Heteroplastic Bone and Cartilage in the Female Genital Tract.**

By A. B. Gerbie, R. R. Greene and R. A. Reis. *Obstet. Gynec.*, **11**, 573–578. May 1958. 5 figs. 21 refs.

Heteroplastic ossification or cartilage formation rarely occurs in the female genital tract except as a component of tumours. The authors present brief histories of 7 instances of heteroplastic ossification and 1 of heteroplastic cartilage formation in the female genital tract. Chronic inflammation and/or endometriosis may serve as the stimulus for the heteroplastic process.

J. G. Dumoulin

INFECTIONS OF THE REPRODUCTIVE ORGANS

329. **Tetracycline in the Form of Gynaecological Tablets.** (Le tetracycline en comprimes gynécologiques.)

By E. Sarlin and R. Marty. *Gynéc. prat.*, **9**, 109–114. 1958.

The frequency of leucorrhoea as a gynaecological symptom is only equalled by the number of therapeutic substances which are available to treat it. This article deals only with leucorrhoea associated with cervicitis or vaginitis.

After diagnosis, all forms of cervicitis and vaginitis, except monilial vaginitis, have been treated with a 10-day course of 100 mg. tablets of tetracyclin chlorhydrate administered vaginally. On account of a fairly frequent mild pruritus, the authors have found it advisable to divide this 10-day course into two 5-day periods with a 5-day interval intervening. They claim cures in 52 of 92 assorted cases so treated. Cures were assessed by examination 2 to 3 weeks after the end of the course.

In 10 cases intolerance developed and there were 8 failures. The remainder of the patients are classified as "improved".

It is claimed that this therapy is of special use in the treatment of cervicitis when it is combined with diathermy coagulation.

Geoffrey Dixon

330. **Vulvovaginitis in Infertility Practice.** (Vulvovaginites dans une consultation pour le traitement de la sterilité.)

By O. Blanchard. *Gynéc. prat.*, **9**, 13–14. 1958.

In a series of 455 infertile couples investigated between the years 1950 and 1955 in an infertility clinic in Buenos Aires, 35 of the female partners (7·7 per cent) were found to be suffering from vulvovaginitis. In one case this was due to monilia, in the others the trichomonas vaginalis was responsible. The women were aged between 22 and 35 years.

The author presents his views on diagnosis and treatment which follow orthodox practice. He states that all these 35 cases showed another cause capable of explaining the infertility and that vulvovaginitis should not be considered the fundamental cause of infertility. Nevertheless, it may be a contributory factor and should always be treated whilst further investigation is proceeding.

Geoffrey Dixon

331. **The Curative Treatment of Human Genital Trichomoniasis by Multiple Local Treatments.** (Le traitement curatif de la trichomonase génitale humaine. Traitement local multiple.)

By J. M. Bedoya and J. M. Fernandez-Ortega. *Gynéc. prat.*, **9**, 97–103. 1958. 5 refs.

The authors emphasize the importance of their previously published work showing that the trichomonas can always be found not only in the vagina but also in the urethra of the females harbouring it, and in the genital tract of their male partners.

It is, they claim, useless to treat the infestation by intra-vaginal therapy alone. Oral therapy has been most disappointing in their hands, and they therefore recommend local treatment of all known places of infestation. The necessity for simultaneous treatment of both partners is stressed, and treatment must also make allowance for extra-marital "partners". The treatment they recommend consists, in the male, of the insertion of specially prepared "pencils" of 2·5 grams of stovarsol, each 10 cm. in length, into the urethra. This is performed each morning and each night after emptying the bladder. Micturition is delayed for as long as possible after the insertion.

The treatment in the female is similar, but the "pencils" are 5 cm. in length and contain only 1·2 grams of stovarsol. At the same time an arsenical pessary is inserted high into the vagina. This therapy is maintained in both sexes for seven days.

At the time of writing they had treated 23 couples and 8 additional females. The cure of a female is considered complete when repeated examinations have been negative for trichomonas for a period of more than 5 months after treatment. The male is considered cured only when normal coitus has occurred during the time of observation of his partner. The results obtained in the 31 women involved are:

Complete cure (more than five months)	11 cases
Provisional cure (less than five months)	9 cases
Therapeutic failures	7 cases
Patients lost from sight	4 cases

Explanations are given for the failures of therapy. The authors admit that this method of treatment presents many practical difficulties, but nevertheless they consider it the most effective they have so far used.

Geoffrey Dixon

332. **The Oral Treatment of Human Genital Trichomoniasis with 2-Amino-5-Nitrothiazol (Tritheon) and with Trichomycin.** (Le traitement oral de la trichomonase génitale humaine par le 2-amino-5-nitrothiazol (Trithéon) et par la trichomycine.)

By J. M. BEDOYA and J. M. FERNANDEZ-ORTEGA. *Gynéc. prat.*, **9**, 91–96. 1958. 9 refs.

Five in-patients suffering from trichomoniasis were treated for eight days by the oral administration of three tablets of "Tritheon" daily. Two days later it was found in wet films taken from all the five patients.

Two couples and two young girls suffering from the same infestation were treated with the antibiotic trichomycin which is derived from a Japanese mushroom. They were given 50,000 units orally thrice daily for ten days. At the end of this time the parasite was found in all cases. The authors expressed their surprise at the previous reports of beneficial results from several authors and are dismayed by the publicity that they have received. They suggest that these reports may have been due to inadequate tests of cure. Some authors have invalidated their results by combining the oral use of these two agents with some other local therapy.

Geoffrey Dixon

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

333. **The Problem of Invasive and Non-Invasive Carcinoma of the Cervix and of Pre-Cancerous Conditions in the Light of Histochemical Studies.** (Das Problem des präinvasiven und invasiven Kollumkarzinom und der sog. "präkanzerösen Zustände" im Lichte der histochemischen Untersuchungen.)

By A. BIELECKI. *Zbl. Gynäk.*, **80**, 743–750. May 10, 1958. 13 figs. 12 refs.

The author studied the concentration of desoxyribonucleic acid (DRN) in the chromosomes of the epithelium of the portio, with the object of detecting any possible quantitative difference in the dynamics of cellular mitosis between invasive and non-invasive cancers. The staining method of Feulgen and the Schiff reagent were used.

There were 20 cases in each group. The DRN content was increased to about the same degree in both types.

In one other patient with "paratypical" changes in the portio the DRN content was very high and approached the level of cancers. In this patient an intra-epithelial carcinoma developed 5 months later.

The author concludes that there is no detectable difference between invasive and non-invasive cancers as regards the dynamics of cellular division.

Bruce Eton

OPERATIONS

334. **Diagnostic Pneumo-Gynaecography.** (L'associazione celioscopia e pneumo-ginecografia nella diagnostica ginecologica.)

By C. DURANDO and M. FACCINI. *Minerva ginec., Torino*, **10**, 187–203, Mar. 15, 1958. 26 figs. 29 refs.

Visual aids to gynaecological diagnosis, in addition to the colposcope, include the coelioscope and the hysterosalpingogram. Furthermore, radiological visualization of the female pelvic organs can be facilitated by inflating the peritoneum abdominally with oxygen; the patient is then put in a 30° prone Trendelenberg position which, after displacing the intestines, fills the pelvis with gas. Two pictures are taken, the first at right angles to the inclined table, the other vertically downwards. This method can be combined with hysterosalpingography in the usual way, but, as the plates show, the latter adds but little in many cases. The coelioscope is of course used after oxygen inflation with the patient in the supine Trendelenberg position, and is of special value in the diagnosis of tuberculous salpingitis. Using these methods with an occasional pelvic phlebography for good measure, the authors examined 212 patients for a variety of pelvic disorders, including tuberculous salpingitis, microcystic ovaries, dermoid cysts and salpingo-oöphoritis, and have illustrated the results with a good series of skiagrams and a coeliogram in colour. The technique is clearly described.

W. C. Spackman

335. **Intra-Aortic Transfusion: Discussion of Technic and Report of Five Cases.**

By H. L. RIVA, J. L. BREEN, R. P. HATCH and W. L. PICKHARDT. *Obstet. Gynec.*, **11**, 537–542. May 1958. 3 figs. 2 tables. 21 refs.

The authors present 5 cases in which an intra-aortic blood transfusion was given for shock and haemorrhage because intravenous therapy was not adequate. Approximately 500 ml. of blood brought about a rapid change in all patients within 5–20 minutes. This method produces a rapid perfusion of the coronary and cerebral vessels which is its most important asset.

The transfusion is accomplished in a few minutes with a regular intravenous set and an angled needle. The needle is introduced into the aorta just above its bifurcation after vertically splitting the posterior peritoneum. In no case was it necessary to repair the aorta following transfusion and no retroperitoneal haematomas were observed.

J. G. Dumoulin

336. **The Operative Treatment of Prolapse of the Blind-Ending Vagina.** (Zur Operation des Prolapses der blind endigenden Scheide.)

By J. SEDERL. *Geburtsh. u. Frauenheilk.*, **18**, 824–829. June 1958. 4 figs. 9 refs.

The author describes 2 operations devised by Amreich (but hitherto unpublished) for treating inversion of the vagina following total hysterectomy. The blind end of the vagina is fixed to one of the sacro-spinous ligaments.

In the first operation (Amreich I) the patient is placed in the right lateral position. Through a mid-line incision the coccyx is excised. The insertion of the levators is divided so that the pelvic surface of the left levator ani muscle is exposed. The rectum is pushed over to the patient's right side. By pressure from the vagina the blind end is pushed backwards so that it presents in the wound and the fascia over it is dissected off. The blind end of the vagina is sutured to the exposed left sacro-spinous ligament. A drain is inserted and the levators are brought together in the mid-line.

For the Amreich II operation the patient is in the lithotomy position. A mid-line incision is made in the posterior vaginal wall to expose the rectum, which is pushed to the left. By blunt dissection the rectum is separated from the pelvic cellular tissue to expose the right sacro-spinous ligament. Two or 3 silk sutures are passed through the sacro-spinous ligament and the blind end of the vagina. If there is a cystocele these sutures are left untied until an anterior colporrhaphy has been performed. The incision in the posterior vaginal wall is then closed by a colpo-perineorrhaphy.

The author states that he has performed both operations successfully, but he gives no details of his results.

Peter J. Huntingford

337. **The Operative Treatment of Cervical Incompetence.** (Zur operativen Behandlung der Insuffizienz des inneren Muttermundes und der oberen Zervix.)

By K. J. ANSELMINO. *Geburtsh. u. Frauenheilk.*, **18**, 797–805. June 1958. 7 figs. 11 refs.

The author discusses cervical incompetence as a cause of habitual abortion. He distinguishes between primary cervical incompetence (a neurogenic dysfunction often associated with endocrine disorders or congenital malformations of the uterus) and secondary cervical incompetence following forcible dilatation, amputation or conization of the cervix. He recommends operative treatment for this latter group of traumatic cases. They can be distinguished from the first group by the history, and on examination a No. 8 Hegar's dilator is easily passed through the internal cervical os. The different techniques of operative repair that have been used are described. The author himself has performed the operation of Cooperman and Lash (excision of an elliptical wedge of tissue from the upper cervix so that the external os and the cervical mucosa remain intact) on 6 occasions. Three of these patients have subsequently conceived and successfully carried children to term. Finally the methods used for treatment of this condition during pregnancy are discussed and here the work of Green-Armytage and McDonald is quoted.

[This is an admirable brief review of the surgical techniques in use at the present time for the treatment of cervical incompetence.]

Peter J. Huntingford

338. **Puerperal Sterilization.**

By C. MEHTA and A. MEHTA. *J. Obstet. Gynaec. India*, **8**, 199–213. Mar. 1958. 4 figs. 16 refs.

A review is made by the authors of all cases of sterilization by tubal ligation in a private hospital over a twelve-year period, ending in 1956. The operation was scarcely ever performed in India before that time. The indications were obstetric, medical, eugenic, and socio-economic, the last mentioned indication being by far the commonest. Moreover, as time went on, the number of cases sterilized annually increased but the proportion done for medical and obstetric reasons diminished. Sterilization was not done for multiparity, unless the woman had four deliveries, of which two of the children were sons.

Of 3,888 patients delivered, 7·3 per cent were sterilized. A modified Pomeroy technique was employed, and no failure was reported. Spinal anaesthesia was preferred, and the operation was done within 48 hours of delivery.

A questionnaire sent to all cases elicited 116 replies. It seemed that menstrual disturbances occurred in 32 per cent of cases, but that these were cured by curettage. Morbidity in the puerperium occurred in 15 per cent of cases.

[It seems unusual that so many women were sterilized for socio-economic reasons in a private hospital.]

John McKiddie

339. **A New Operation for Stress Incontinence.** (Wlasny sposob operacyjnego leczenia moczenia mimowolnego u kobiet podczas wysilku.)

By M. PROCHOROW. *Ginek. polska*, **29**, 157–166. 1958. 9 figs. 23 refs.

After critical analysis of all the methods for the cure of stress incontinence, the author describes his own procedure. It consists of tightening of the urethra by two skin flaps cut from the labia minora, and put through an artificially created subcutaneous tunnel around the urethra. The merit of the method lies in the simplicity of the operation and the great percentage of cure.

The author has operated on 25 cases, the ages being 20 to 80 years, with a complete cure of stress incontinence.

S. H. Riterband

NOTICES

THE JOURNAL OF OBSTETRICS AND GYNAECOLOGY OF THE BRITISH EMPIRE is published under the direction of the Royal College of Obstetricians and Gynaecologists. All business correspondence should be addressed to the *Journal of Obstetrics and Gynaecology of the British Empire*, 58 Queen Anne Street, London, W.1.

SUBSCRIPTION RATES

The Journal is published bi-monthly on or about the 21st of February, April, June, August, October, December and the Annual Subscription rates, due on 1st January, covering 1 volume (6 issues) are:

	£	s.	d.
Great Britain, Northern Ireland and Eire	3	5	0
Dominions, Colonies and Foreign Countries: Surface Mail	3	15	0
Air Mail	8	2	6

Subscriptions are only accepted for complete volumes.

Remittances are payable to:

The Journal of Obstetrics and Gynaecology of the British Empire,
58 Queen Anne Street, London, W.1.

Banker's Orders should be made payable to the Journal account at Barclays Bank, Vere Street, Cavendish Square, London, W.1.

Overseas payments should be by Banker's draft payable at sight in London.

EDITORIAL NOTICES

The Editor is: Professor James Young, *D.S.O.*, M.D., F.R.C.S., F.R.C.O.G., Paynes Hill House, Steeple Aston, Oxford.

PUBLICATION

Original articles for publication are invited and should be sent to the Editor. They are considered for publication on the understanding that they are contributed to this Journal solely. Reproduction elsewhere, in whole or in part, is not permitted without the previous written consent of the Author and Editor, and the customary acknowledgments must be made. The Royal College of Obstetricians and Gynaecologists cannot be held responsible for the views expressed in the Journal.

Blocks will normally be held by the Printers for two years after which they will be destroyed.

BOOKS FOR REVIEW

Books for review should be sent to the Editor, Professor James Young, Paynes Hill House, Steeple Aston, Oxford.

Directions to Contributors

Authors are advised to keep a copy of all manuscripts. Proofs will be submitted to authors resident in the United Kingdom, but to avoid delay or loss the proofs of authors resident abroad will be corrected by the editorial staff, unless the authors wish to delegate the work to a representative in this country.

PRESENTATION OF MANUSCRIPT

Double spaced typescript (not carbon copies) should be submitted. Italics in the text should in general be reserved for words in a foreign language and as little as possible used to indicate emphasis.

Proper scientific names giving both genus and species should be italicized, with an initial capital and contraction for the genus only after a full spelling at the first mention, thus:

Clostridium welchii followed by *Cl. welchii; Escherichia coli—E. coli; Mycobacterium tuberculosis—Myco. tuberculosis; Corynebacterium diphtheriae—C. diphtheriae.*

Each sentence should have its proper components thus:

"*Progress:* The patient continued to improve," NOT

"*Progress:* Went downhill."

The author's name, his decorations, degrees and relevant diplomas should appear at the head of the paper together with his appointment at the time of preparation of the text.

TABLES AND ILLUSTRATIONS

Where possible line drawings are preferred to photographic pictures or half-tone drawings. Elaborate tables should be so prepared that they can be reproduced photographically.

Tables should be numbered in Roman numerals (Table I, Table II, etc.) and set out on sheets separate from the text, with indications as to where the author desires them to be placed. Illustrations, too, should be kept separate from the text and numbered in Arabic numerals, Fig. 1, Fig. 2, etc. Each figure should have a reference in the text and a descriptive legend to be printed underneath. This legend should be typed on an attached sheet and not written on the back of the illustration. The lines in charts should not be in colours but in black, and when graph paper is used the ruling should be grey or faint blue and *not* brown, red or green. The magnification of microscopical illustrations should be stated (e.g. ×250). X-ray films should not be submitted unless the author is not in a situation to have these printed, when the Journal will undertake to have this done. If the films promise poor reproduction the author is advised to send line tracings of the appearances instead. Authors may be required, at the Editor's discretion, to contribute to the cost of reproducing tables and illustrations.

ABBREVIATIONS

These should be avoided as far as possible. "Per cent" should be used instead of the symbol "%" and such forms as T.B., R.B.C., B.P., P.E.T., A.P.H. eschewed.

Dates should be given as 10th May, 1946, and *not* 10.V.46. Numbers should be in the form of numerals and not words except when beginning a sentence, thus "Fifteen patients out of a total of 60 exhibited," etc. The official rather than the proprietary names of drugs must be used. The Journal convention is gr. for grains; g. for grammes; Kg.; ml. (*not* c.c. or c.cm.); mg.; pounds (*not* lb.); ounces (*not* oz.), etc., and wherever suitable the metric equivalent of an English measure should be given, for example, when recording pelvic measurements, size and weight of babies, tumours, etc.

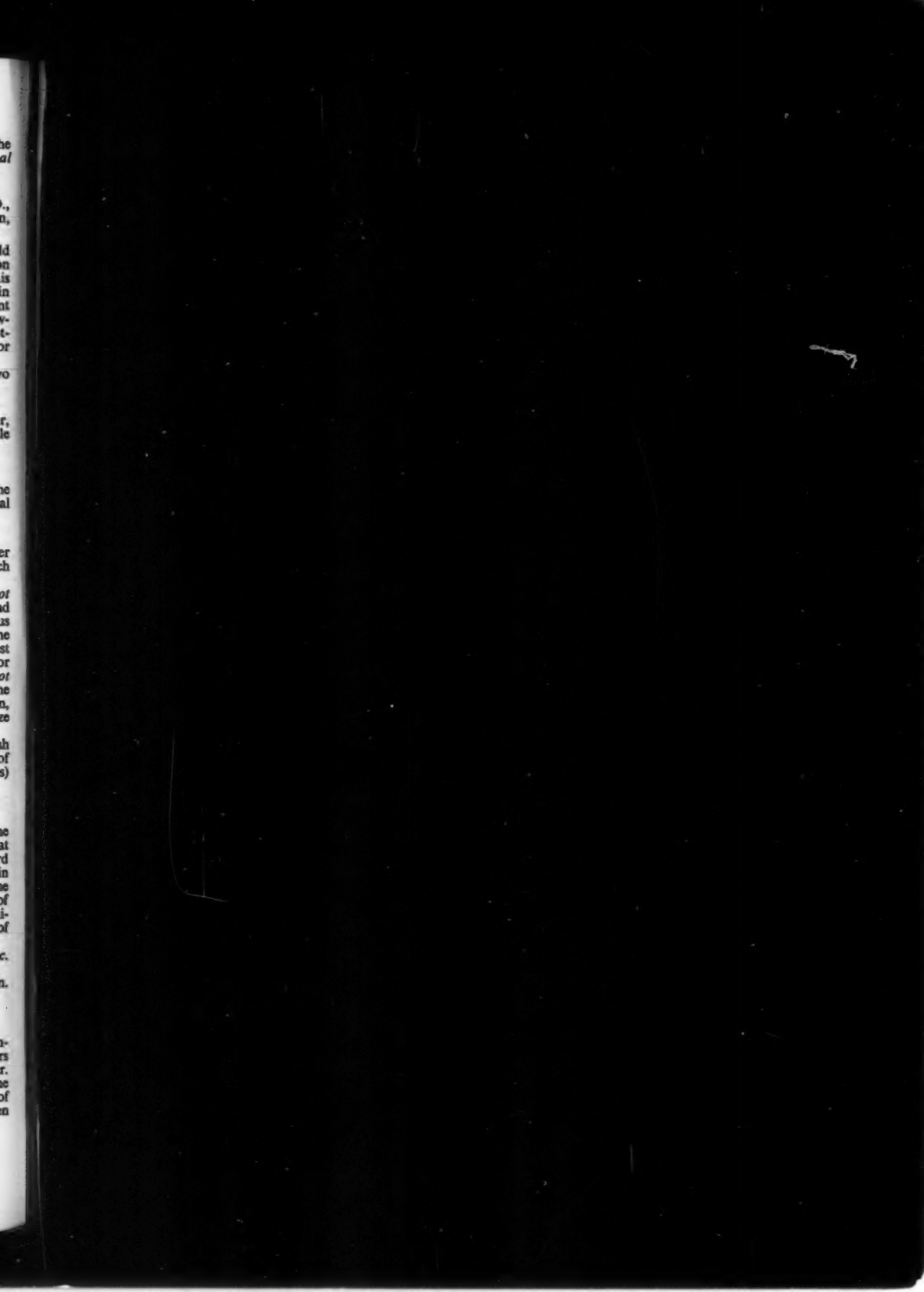
When comparable figures are given, either the English or the metric mode must be followed, thus: the excretion of urine/24 hours should be shown in ml. (and not ounces) when the urinary or blood-urea is given in g./100 ml.

REFERENCES

In the text the author's name should be given, with the date of publication and the list of authors quoted put at the end of the text in alphabetical order as in the Harvard Scheme: Author's name, initials, year of publication (in brackets), name of journal (*italics* abbreviated), volume number (underlined) and page number. In the case of books the order is: Author's name, initials, year of publication, full title (*italics*), edition, publisher and place of publication, page, thus:

Brown, H. E., and Jones, B. K. (1943): *J. Obstet. Gynaec. Brit. Emp.*, **2**, 128.

Sampson, P. (1940): *Obstetrics for Midwives*. 2nd edition. Fraser, London. p. 9.

REPRINTS

The issue of free reprints to contributors is discontinued, but a copy of the issue in which the article appears will be sent to any contributor who is not a subscriber. Reprints can be purchased by arrangement with the printers if application is made when the corrected proof is returned or, in the case of overseas contributors, when the manuscript is submitted.